Amendment

Protocol Number: 12C0068-H **Reference Number:** 366337

Principal Investigator: Steven Pavletic NCI ETIB 301.402.4899 pavletis@mail.nih.gov

(NIH Employee Name, Institute/Branch, Telephone and e-mail)

Protocol Title: A Randomized Double-Blind Pilot Study of Topical Clobetasol 0.05% Oral rinse for Oral Chronic Graft-Versus-Host Disease

SIGNATURES

Principal Investigator (*):
Steven Pavletic - applied signature on 01/31/2017 4:02 PM EST

Accountable Investigator:
PI is the Accountable Investigator

Branch Chief/CC Department Head (**):
Ronald Gress - applied signature on 01/31/2017 9:59 AM EST

Medical Advisory Investigator (if applicable):
N/A

Lead Associate Investigator signature:
N/A

Referral Contact signatures:
N/A

Associate Investigators signatures:
N/A

For Institute/Center Scientific Review Committee:
N/A

Other IC Clinical Director signatures:
N/A

APPROVALS

IRB Chair:
Michael Hamilton - applied signature on 02/14/2017 10:19 AM EST

Clinical Director:
N/A

CONCURRENCE

OPS Protocol Specialist:

Lemuel Clayborn	AM H	02/28/2017
Signature	Print Name	Date

* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: Expedited

DEC Clearance Date: NA

Protocol Version Date: 01/24/2017

Abbreviated Title: Clobetasol rinse for oral cGVHD

NCI Protocol #: 12-C-0068 H

Version Date: January 24, 2017

Title: A Randomized Double-Blind Pilot Study of Topical Clobetasol 0.05% Oral rinse for Oral Chronic Graft-Versus-Host Disease

Principal Investigator: Steven Z. Pavletic, MD, MS, ETIB, NCI[A-F]
10 Center Drive, CRC 3-3330
Phone: 240-760-6174
E-mail: pavletis@mail.nih.gov

Lead Associate Investigator: Jacqueline Mays, DDS, PhD, NIDCR[A-F]

Associate Investigators:

Brenna Hansen, RN, OCD, CCR, NCI[A,B,C]

Stephanie Cotton, RN, OCD, CCR, NCI[A,B,C]

Daniele Avila, MSN, CRNP, ETIB, NCI[A,B,C]

Richard Childs, MD, NHLBI[A,B,E,F]

Bazetta Blacklock-Schuver, RN, OCD, CCR, NCI[A,B,C]

William Figg, PharmD, GMB, CCR, NCI[B,E,F]

Daniel Fowler, MD, ETIB, NCI[A-F]

Ronald Gress, MD, ETIB, NCI[A-F]

George Grimes, RPh, CC[B]

Jennifer Mann, CRNP, ETIB, NCI[A,B,C]

David Kleiner, MD, LP, CCR, NCI[B,E,F]

Sandra Mitchell, PhD, CRNP, ORB, NCI[E,F]

Tracey Chinn, RN, ETIB, NCI[A,B,C]

Fran Hakim, PhD, ETIB, NCI[E-F]

Nataliya Buxbaum, MD, ETIB, NCI[A-F]

Seth Steinberg, PhD, OCD, CCR, NCI[E-F]

Ellen Carroll, RN, OCD, CCR, NCI[A,B,C]

Lauren Curtis, MD, ETIB, CCR, NCI[A-F]

Non-NIH Associate Investigator: Lauren Skeffington, PA, Leidos Biomedical Research, [A,B,C]

Referral Contact: Steven Z. Pavletic, MD

Study Coordinator: Bazetta Blacklock-Schuver, RN, OCD, CCR, NCI[A,B,C]
Telephone: 240-760-6156
Fax: 301-451-5578
Email: bblacklock@mail.nih.gov

Investigator Roles:

A. *Obtain information by intervening or interacting with living individuals for research purposes*
B. *Obtaining identifiable private information about living individuals*
C. *Obtaining the voluntary informed consent of individuals to be subjects*
D. *Makes decisions about subject eligibility*
E. *Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes*
F. *Studying, interpreting, or analyzing de-identified data or specimens for research purposes*
G. *Some/all research activities performed outside NIH*

Investigational Agents:

Drug Name:	Clobetasol
IND Number:	77313
Sponsor:	Center for Cancer Research
Manufacturer:	Spectrum Chemicals

PRÉCIS

Background:

- Chronic Graft versus Host Disease (cGVHD) is a major late complication of allogeneic hematopoietic stem cell transplantation.
- The oral cavity is the second most commonly affected area in cGVHD and is a major cause of morbidity.
- Clobetasol is a high-potency topical corticosteroid widely used for a variety of inflammatory disorders of the skin and oral mucosa.
- Treatment of oral cGVHD by topical agents is an attractive strategy to potentially avoid adverse effects associated with systemic immunosuppression.

Objective:

- To investigate efficacy of topical clobetasol 0.05% oral rinse for oral chronic graft-versus-host disease (cGVHD)

Eligibility:

- Patients age 12-99 years with clinically significant oral cGVHD.

Design:

- This is a randomized, double blind, placebo-controlled, pilot study of clobetasol 0.05% topical oral rinse with an open label extension period.
- Patients will rinse oral cavity with 10cc of clobetasol 0.05% or placebo oral rinse for 2 minutes 3 times a day.
- Treatment duration will be for 2 weeks in the randomized phase and 2-4 weeks in the open label phase.
- Up to 40 patients will be enrolled on this pilot trial until 34 evaluable patients are assessed.

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INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To investigate efficacy of topical clobetasol 0.05% oral rinse for oral chronic graft-versus-host-disease (cGVHD) during a four-week treatment period as assessed by Oral Mucositis Rating Scale (OMRS).

1.1.2 Secondary Objectives

1.1.2.1 To assess the effect of topical clobetasol on oral cGVHD related pain, sensitivity, and dryness.

1.1.2.2 To evaluate the basic pharmacodynamics and pharmacokinetics of clobetasol mouth rinse in cGVHD patients.

1.1.2.3 To obtain a pilot assessment of patient perceived oral health in cGHVD and its response to treatment with topical clobetasol.

1.1.2.4 To evaluate the validity of the NIH Oral cGVHD Clinical Scoring instrument.

1.1.2.5 To evaluate the immunological profile present at baseline and after clobetasol treatment in oral tissue to identify potential biomarkers for disease response or resistance to clobetasol.

1.1.2.6 To evaluate blood and saliva to identify potential biomarkers for oral cGVHD disease activity and response to topical clobetasol.

1.2 BACKGROUND AND RATIONALE

1.2.1 Chronic Graft-Versus-Host-Disease

Allogeneic hematopoietic stem cell transplantation (alloHSCT) has been used increasingly for malignant and non-malignant disorders [1]. Graft-versus-host disease (GVHD) is a major complication and a leading cause of morbidity and mortality in recipients of alloHSCT. GVHD results from immunologic attack by the donor's immune cells on the recipient's tissues and organs. Incidence and severity of GVHD vary depending on degree of mismatch of major histocompatibility antigens of the donor and host, age of donor and recipient, source of stem cells, and type of preparative regimen[2]. Development of non-myeloablative conditioning regimens has led to a decrease in early post-transplant mortality and an increase in chronic GVHD (cGVHD). Almost 70% of patients who survive more than 100 days after alloHSCT will develop cGVHD, with the majority manifesting in the first year.[2-5] The undersupply of related donors led to expanded use of unrelated and partially matched unrelated donors. Use of non-myeloablative conditioning regimens is related to more frequent use of both older donors and recipients[6]. Taken together, these factors have increased the incidence of cGVHD.

Chronic GVHD has many similar features of autoimmune diseases, such as lupus, lichen planus, and scleroderma, and can have a varied clinical presentation. Mononuclear cellular infiltrates are found in many areas of the graft recipient, including the liver, skin, oral mucosa, and salivary glands[7]. Recent NIH consensus conferences proposed new criteria for staging of cGVHD that consider extent of the disease, number of involved organs, and severity of functional

impairment[2,8,9]. Some of these criteria have been validated, and others require validation in future trials[2,4,8,10-12]. Chronic GVHD can persist for months to years and requires long-term multidisciplinary management.

1.2.2 Oral involvement in cGVHD

Oral cGVHD is a common, major cause of morbidity and decrease in health-related quality of life (HRQOL) in long-term alloHSCT survivors[10,13-15]. In a recent randomized trial of peripheral blood stem cell (PBSC) vs. bone marrow stem cells (BMSC) transplants, oral mucosal changes were the most common manifestation of cGVHD in BMSC recipients and the second most common (after skin) in PBSC transplants. Overall incidence in cGVHD was around 85%[3]. Oral manifestations of cGVHD include lichen planus-like changes, mucosal atrophy and ulcerations, taste disturbances, and salivary gland hypofunction. Oral pain and food sensitivity are common, and not limited to patients with ulcerations[10,16,17]. Oral discomfort was shown to be associated with decrease in food intake and weight loss in this group of patients[10,18]. Recently, the contribution of oral cGVHD to inferior health-related QOL was reported [10,19]. There have been several reports of increased incidence of oral squamous cell carcinoma (SCCA) after allo-HSCT, with history of oral cGVHD identified as an independent risk factor[20,21].

1.2.3 cGVHD Therapy

1.2.3.1 Systemic and topical corticosteroids

The treatment for cGVHD consists of various systemic immunosuppressive agents, most commonly systemic corticosteroids, cyclosporine, tacrolimus, mycophenolate, sirolimus and phototherapy[9]. Long-term immunosuppressive treatment for GVHD has a variety of serious complications including life-threatening infections, aseptic bone necrosis, hypertension, and secondary diabetes.[6,22]

Corticosteroids are the most commonly used systemic treatment of both acute and chronic GVHD. Immunosuppressive and anti-inflammatory effects of corticosteroids are mediated through multiple mechanisms including immune cell apoptosis and interference with dendritic cell maturation. The critical role of dendritic cells in the development of GVHD has been outlined in several studies. One study demonstrated the potential of GVHD prevention via depletion of host antigen presenting cells in a murine model.[23]. In another animal study, local depletion of Langerhans cells in skin prevented GVHD. Corticosteroids have been shown to prevent development of dermal dendritic cells *in vitro*.[24]. Additionally, topical corticosteroids induced apoptosis in the murine epidermal Langerhans cells and $CD8^{+}$T cells[25].

Topical corticosteroids such as dexamethasone 0.01% oral rinse and clobetasol 0.05% ointment are used widely for treatment of oral cGVHD, although their efficacy has not been formally evaluated in this condition[4]. Ointments and creams have a disadvantage of uneven and cumbersome application, furthermore, it is difficult to estimate the systemic versus local effect. Unlike solutions used as rinses, ointments can be easily swallowed and absorbed through the gastrointestinal tract. At the NIH Clinical Center, both dexamethasone oral rinse and clobetasol ointment have been used with variable success. In general, complicated application procedures reduce compliance and make evaluation of response difficult. Oral rinses have a particular advantage when a significant oral cavity area is affected as the contact with the entire surface is ensured with potential decrease in systemic absorption.

1.2.3.2 Clobetasol

Clobetasol is a readily available corticosteroid used topically in a wide variety of inflammatory conditions. Clobetasol 0.05% ointment is FDA approved for the treatment of inflammatory skin diseases and clobetasol spray is approved for psoriasis. Clobetasol ointment is widely used topically by oral medicine practitioners for the treatment of oral ulcerative conditions including oral lichen planus, a condition clinically and pathologically similar to oral cGVHD and has been shown to be safe and effective[26-28]. When used 2 times a day for 4-8 weeks, the response rates exceeded 90%.[28,29] There are few side effects associated with oral topical corticosteroid use with the most common being oral candidiasis. To reduce incidence of oral candidiasis infection, patients will be asked to swish and spit once per day with nystatin (100,000u/ml) rinse, which is a standard preventative measure in high-risk patients. Although there have been reports of adrenal suppression associated with high potency topical steroids, these were generally rare and occurred primarily in young children and in patients with large surface areas of involvement (skin). In one study, no changes in morning cortisol levels were observed when clobetasol was applied topically in the oral cavity for 2 months for oral lichen planus.[23] However, other reports have indicated signs and symptoms of adrenal suppression in patients with severe erosion of the oral mucosa, as in erosive oral lichen planus, and long term use (years) of topical clobetasol[30,31]. The effect of clobetasol and other steroids applied topically in the oral cavity on the ability of adrenal glands to respond to stress levels of ACTH has not been formally evaluated in cGVHD or in normal patients.

1.2.4 Trial Plan

Treatment of oral GVHD by topical agents is an appealing strategy because it would potentially avoid the adverse effects associated with systemic immunosuppression and reduce systemic exposure to glucocorticoids. Most importantly, using immunosuppressive agents locally would concentrate the treatment effects for potential maximum benefit. Conversely, use of systemic agents for the same purpose would interfere not only with the undesirable GVH response, but also with immune responses directed against the malignancy (the graft vs. tumor effect), which is the principal mechanism through which reduced intensity transplants achieve sustained disease remission.

Therefore, we propose this pilot randomized double blind placebo controlled trial of topical clobetasol 0.05% oral rinse for oral cGVHD. Consenting subjects with clinically significant oral cGVHD will be randomized to receive clobetasol or placebo oral rinse for 2 weeks. All subjects will be evaluated biweekly. Clinically significant oral cGVHD is defined as a score of 20 or greater on the Oral Mucositis Rating Scale (OMRS) based on the patient cohort (over 250) seen in the NIH natural history of cGVHD protocol. At the first 2 week appointment, patients will be unblinded and subjects randomized to placebo will be assigned to additional 2-4 week open label treatment period with topical clobetasol rinse. All patients will therefore complete 4 weeks of treatment with the study drug (2 additional weeks for patients originally assigned to clobetasol arm and 4 weeks for patients assigned to placebo arm). All patients will be reevaluated 1 month following the open label period to evaluate the response and collect follow-up data.

Patients with progressive disease while on the clobetasol treatment as determined at any scheduled evaluation visit will be considered non-responders for the primary endpoint evaluation and will be taken off-study. Within 90 days of the end of the open label treatment period, all patients with evidence of benefit (response or stable disease) will be given an option to continue treatment with clobetasol 0.05% with or without additional treatment as deemed clinically necessary, up to one month. The proportion of responders in the active and placebo arm will be used as the primary outcome variable. As no standard definition of oral cGVHD response exists, for purposes of this pilot study, response will be defined as decrease of 25% or more on the OMRS (**Appendix A**). Difference in OMRS scores between the groups at the end of the 2 week blinded period and the change in OMRS score between beginning and the end of the 4 week treatment period with clobetasol oral rinse will serve as a secondary outcome variables. The study schedule of events is outlined in

Appendix E.

The placebo design is justified by the following: a) there is no proven standard topical therapy for oral cGVHD, b) patients will be unblinded after 2 weeks of treatment (defined in section **3.2.4**) and those on placebo will be allowed to cross over to the alternate treatment arm. This will allow all participants to receive the study drug for 4 weeks.

In addition to potential direct benefit to the cGVHD patients, this study is likely to provide valuable insights into the cellular and molecular alterations associated with the development of cGVHD and treatment with topical corticosteroids. This will lead to better understanding of the pathogenesis of cGVHD needed as the foundation for development of new therapeutic interventions.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Age: 12 years – 99 years.

2.1.1.2 Diagnosis: clinically significant oral cGVHD after allogeneic HSCT with severity score of at least 2 on erythema subset and/or at least 1 on ulceration subset and a composite score ≥20 of the Oral Mucositis Rating Scale (OMRS) scale (**Appendix A**)[12,4] confirmed by the principal investigator (PI), clinical study chair (CSC), or lead associate investigator (LAI).

2.1.1.3 Hematologic Function: Patients must have a platelet count ≥20,000/μL at the time of the initial evaluation.

2.1.1.4 Informed Consent: All patients or their legal representative (for patients <18 years old) must sign an IRB approved informed consent document (cGVHD natural history protocol 04-C-0281 or any NCI protocol allowing for screening procedures) prior to performing studies to determine patient eligibility. After confirmation of patient eligibility all patients or their legal representative must sign the protocol specific informed consent. For pediatric patients age appropriate assent will be obtained in accordance with NIH guidelines.

2.1.1.5 Patients must be able to rinse and expectorate study medication rather than swallow it. Female patients must be willing to practice birth control (including abstinence) during and for two months after treatment, if of childbearing potential.

2.1.1.6 Patients must have the ability and willingness to come to Clinical Center for bi-weekly follow-up appointments.

2.1.1.7 No change in systemic immunosuppressive therapy (type or intensity level) within 2 weeks prior to enrollment.

2.1.1.8 A 7-day washout period is required if patients are currently using another oral topical treatment for mouth lesions. Patients currently using clobetasol oral topical treatment are not eligible for this study.

2.1.2 Exclusion Criteria

2.1.2.1 Documented hypersensitivity to clobetasol.

2.1.2.2 Use of clobetasol ointment intra-orally at any time during the last 6 weeks period.

2.1.2.3 Pregnant or breast-feeding females due to possible toxicity to the fetus or infant.

2.1.2.4 Inability to understand the investigational nature of the study to provide informed consent.

2.1.2.5 Patients who, for medical or other reasons, are unable to comply with the study procedures.

2.2 SCREENING EVALUATION

2.2.1 Evaluation outlined in section 3.4.1 and Appendix A.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) <ncicentralregistration-l@mail.nih.gov>. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. Voicemail is available during non-working hours.

2.4 RANDOMIZATION (OR STRATIFICATION) PROCEDURES:

Dr. Steinberg will create the randomization lists using variable block sizes. Patients will be randomized with a single stratification factor to try to ensure a balanced distribution among those getting placebo or not initially: being identified as having a high intensity of immunosuppression (2 or more agents/modalities ± prednisone≥0.5 mg/kg/day) vs. no or a lesser intensity of systemic immunosuppression according to the Intensity of Immunosuppression Scale[10].

Once patients have been evaluated and meet all eligibility requirements, patients will be registered with the NCI Central Registration Office and be randomized to either clobetasol or

placebo. Change of systemic immunosuppressive regimen occurring after enrollment will not be allowed, and if this is necessary during the 2-week blinded phase of the study to control progressive systemic cGVHD, the patient will come off the study. Other medication changes will be documented at the interim or final (end of treatment) appointment and taken into consideration in the final analysis. However, given the small, pilot nature of the study, it is unlikely that the effect of all potential confounders can be meaningfully taken into account.

3 STUDY IMPLEMENTATION

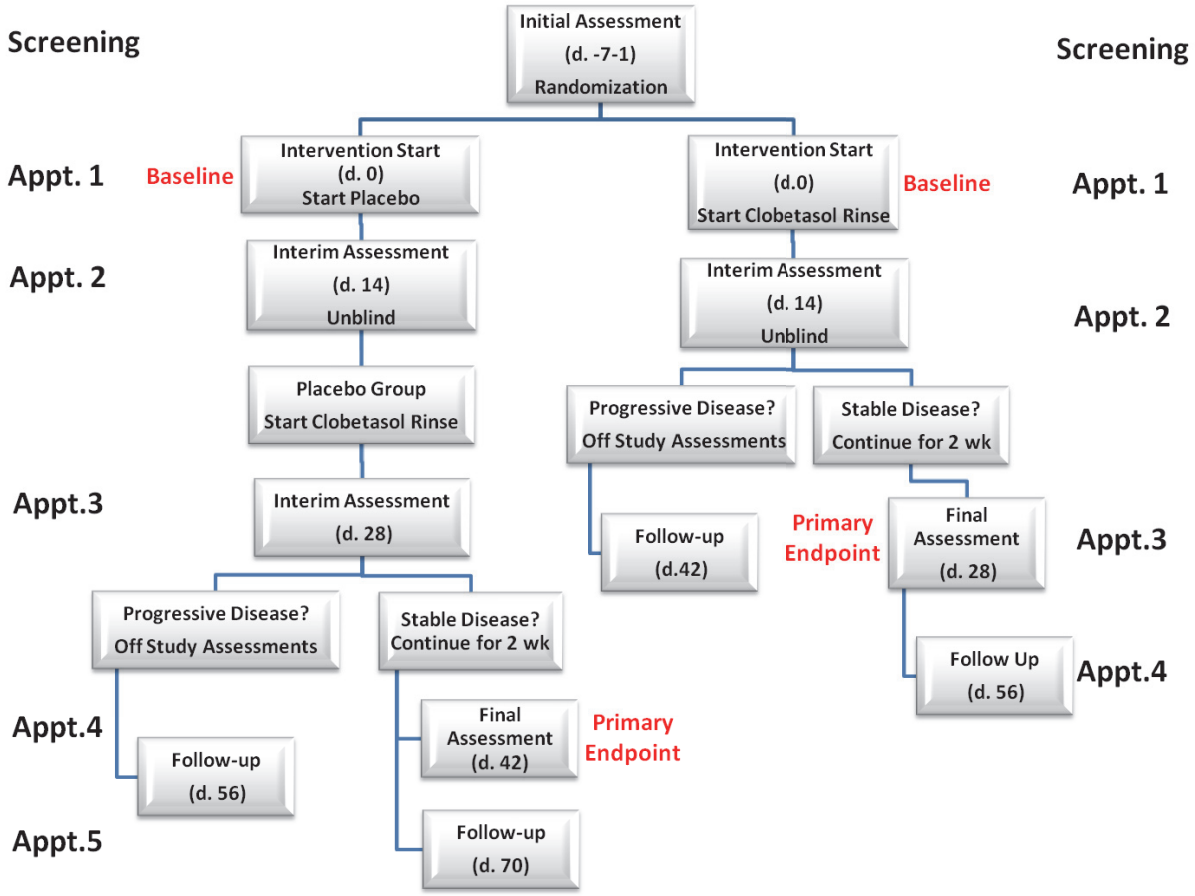
3.1 STUDY DESIGN

This is a randomized, double blind, placebo-controlled, pilot study of clobetasol 0.05% topical oral rinse with an open label cross-over or extension period. Consenting subjects with clinically significant oral chronic GVHD will be randomized to clobetasol 0.05% or placebo oral rinse. The placebo will be flavored with quinine, to approximate the "bitter" taste of clobetasol.

Subjects will be evaluated at bi-weekly intervals while on the study intervention. OMRS score will serve as the primary outcome measure. At the first 2 week interim appointment patients will be unblinded and started on the clobetasol oral rinse open label. In the absence of progressive oral disease on the scheduled interim evaluations during the 4-week clobetasol treatment period, all patients will complete a total of 4 weeks of treatment with clobetasol. Therefore, patients who were originally assigned to clobetasol arm will receive additional 2 weeks of treatment, and patients assigned to placebo arm will undergo an additional 4 weeks of treatment with clobetasol after unblinding. Patients with progressive disease after 2 weeks of therapy with clobetasol will be considered non-responders, taken off-treatment and treated as appropriate in consultation with primary clinician. Within 90 days of the end of the 1 month of treatment, all patients with evidence of benefit (response or stable disease) will be given an option to continue treatment with clobetasol 0.05% with or without additional treatment as deemed clinically necessary for 1 month after the conclusion of the initial treatment period. Additional follow-up appointment will be scheduled for all patients 1 month after completion of treatment. The change in OMRS scores from baseline to 4 weeks of mouth rinse usage will be the primary outcome variable. For the placebo group, the OMRS score at the end of the blinded phase/beginning of clobetasol rinse use (day 14) will serve as the baseline for the primary outcome. Difference in OMRS score between the groups (placebo and clobetasol) at the end of the 14-day blinded phase will serve as a secondary outcome measure. The study schedule of events is outlined in **Appendix G**

For pediatric patients (< 18 years of age at enrollment), ACTH stimulation test and oral biopsy will be done as clinically indicated, and are not required by the protocol. These procedures may still be done for clinical diagnostic and monitoring purposes.

3.1.1 Study Schema



3.2 DRUG ADMINISTRATION

3.2.1 Clobetasol Administration

Clobetasol 0.05% oral rinse and placebo rinse which will be identical in appearance and taste will be labeled and dispensed by the NIH Clinical Center Pharmacy. Subjects will be instructed to rinse oral cavity 3 times daily with the 10 cc of the study medication for 2 minutes and spit out and not to eat, drink, or brush teeth for 30 minutes after the study drug administration. Additionally, the use of oral topical analgesic (viscous lidocaine) will not be allowed for 30 minutes before and after study drug administration.

3.2.2 Duration of Drug Therapy

Patients will be treated with study medication for up to 4 weeks initially. If patients enter the continuation treatment period, they can be treated for up to an additional 4 weeks. Patients may be allowed to enter the continuation treatment period up to 90 days after the last day of treatment.

3.2.3 Progressive disease (as defined in section 6.3.1)

Patients with progressive oral cGVHD after 2 weeks of treatment with the clobetasol oral rinse will be taken off study.

3.2.4 Treatment after 2 week blinded phase

Patients who switch to the clobetasol arm due to initial placebo assignment will be treated with clobetasol 0.05% oral rinse for 4 weeks. Patients originally assigned to clobetasol arm will be treated for another 2 weeks.

3.3 TREATMENT MODIFICATIONS

All dose modifications must be discussed with the PI, or LAI. Given favorable toxicity profile of clobetasol, no treatment modifications are expected. Grade 2 – 3 CTCAE v.4 events attributable to underlying disease and occurring prior to administration of clobetasol will not be reported as an adverse event. These physical findings must be documented at baseline. Expected pre-existing manifestations of cGVHD or systemic steroid therapy may include the following examples: fatigue, colitis, cushingoid appearance, anorexia, dyspepsia, xerostomia, parotid swelling, nausea, taste alteration, arthritis, fibrosis, myositis, osteonecrosis, osteopenia, dry eye, watery eye, pain, dyspnea, vaginal dryness, skin atrophy, alopecia, hyperpigmentation, skin dryness, hypopigmentation, nail changes, photosensitivity, pruritus, rash, and ulcers[12]. In the event of grade 2-3 adverse event attributable to study agent that cannot be easily alleviated without compromising the integrity of the study (such as severe local or systemic hypersensitivity) the subject will be taken off study and treated appropriately as detailed in **Appendix G**.

3.4 PROTOCOL EVALUATIONS

3.4.1 Pre-Treatment Evaluation

Pre-treatment tests should be performed within 1 month prior to enrollment on the trial unless otherwise stated. Evaluation may be performed as part of enrollment onto NIH Protocol #04-C-0281 entitled: "Prospective Assessment of Clinical and Biological Factors Determining Outcomes in Patients with Chronic Graft-Versus-Host Disease." All attempts will be made to enroll patients on this study; however evaluation may be done as part of any ongoing NCI protocol. A 7-day washout period is required if patients are currently using another oral topical treatment for mouth lesions.

1. Optional History and Physical Examination
2. NIH global scoring and data collection, including prior and concurrent therapy, **Appendix H**)
3. Chronic GVHD NIH organ staging
4. Assessment of oral GVHD using OMRS and oral cGVHD Clinical Scoring Instrument (**Appendix A** and **Appendix B)**
5. Numeric rating scales for (0 to 10) for oral pain, oral sensitivity, and oral dryness (**Appendix C**)
6. Oral Global Scale (**Appendix D**)
7. Painometer (POM) Assessment (

8. **Appendix** E)
9. Oral Health Impact Profile- OHIP-14 (**Appendix F**)
10. Hematology: Complete blood counts, with differential and platelet count. Within 72 hours prior to initial evaluation.
11. Chemistries: Electrolytes (including sodium, potassium, chloride, CO2, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, bilirubin, PT/INR and PTT, serum cortisol level and TBNK panel. Within 72 hours prior to initial evaluation.
12. FSH, LH, TSH, T4, CMV by PCR, and HSV by PCR.
13. Urine or Serum Pregnancy test: For all females of childbearing potential. This test is to be performed within 7 days prior to enrollment on the trial.
14. Urine glucose - Within 72 hours prior to initial evaluation.
15. Biopsy of buccal mucosa (4 mm punch) on patient's right side OR of buccal area with GVHD involvement for histopathological examination.
16. Research blood sample collection (18cc)
17. Five minute saliva sample, with and without paraffin stimulation
18. Short ACTH stimulation test, within 1 week prior to initial evaluation.
19. Clinical oral photo series
20. Adrenocorticotropic Hormone blood level within 1 week prior to initial evaluation.
21. Hemoglobin A1C level

3.4.2 Interim Evaluation

Patients should be evaluated at the NIH 14 days after the start of intervention until Day 28 of active rinse use for the following:

1. Optional History and Physical Examination
2. Assessment of oral GVHD using OMRS and oral cGVHD Clinical Scoring Instrument (**Appendix A** and **Appendix B**)
3. Numeric rating scales for (0 to 10) for oral pain, oral sensitivity, and oral dryness (**Appendix C**)
4. Oral Global Scale (**Appendix D**)
5. Painometer (POM) Assessment (**Appendix E**)
6. Oral Health Impact Profile- OHIP-14 (**Appendix F**)
7. Hematology: Complete blood counts, with differential and platelet count

8. Chemistries: Electrolytes (including sodium, potassium, chloride, CO2, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, bilirubin, PT/INR and PTT, cortisol level and TBNK panel.
9. Research blood sample collection (18cc)
10. Urine glucose
11. Five minute saliva sample, with and without paraffin stimulation
12. Clinical oral photo series
13. Optional pharmacokinetic study
14. Hemoglobin A1C level

3.4.3 End of Treatment Evaluation

The following tests and procedures should be performed at the end of scheduled open label treatment period (28 d.) or, if possible, at the time a patient comes off treatment regardless of the reason:

1. Optional History and Physical Examination
2. Assessment of oral GVHD using OMRS and oral cGVHD Clinical Scoring Instrument(Appendices A and B)
3. Numeric rating scales for (0 to 10) for oral pain, oral sensitivity, and oral dryness (**Appendix C**)
4. Oral Global Scale (**Appendix D**)
5. Painometer (POM) Assessment (
6. **Appendix** E)
7. Oral Health Impact Profile- OHIP-14 (**Appendix F)**
8. Hematology: Complete blood counts, with differential and platelet count
9. Chemistries: Electrolytes (including sodium, potassium, chloride, CO2, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, bilirubin, PT/INR and PTT, HSV by PCR, cortisol level and TBNK panel.
10. Urine glucose
11. Research blood sample collection (18 cc)
12. Biopsy of buccal mucosa (4 mm punch) near baseline biopsy site
13. Five minute saliva sample, with and without paraffin stimulation
14. Clinical oral photo series
15. Short ACTH stimulation test
16. Adrenocorticotropic Hormone blood level

17. Hemoglobin A1C level

The goal of the day 28 biopsy is to assess microscopic and molecular changes associated with response (or lack thereof) to topical clobetasol for the purpose of potential cGVHD marker development. The primary response variable in this study is clinical grading of cGVHD.

3.4.4 Follow-up Evaluation

The following tests and procedures should be performed at the end of the scheduled follow-up period (28 days post end of open label treatment period):

1. Optional History and Physical Examination
2. Chronic GVHD NIH organ staging
3. Assessment of oral GVHD using OMRS and oral cGVHD Clinical Scoring Instrument (Appendices A and B)
4. Numeric rating scales for (0 to 10) for oral pain, oral sensitivity, and oral dryness (**Appendix C**)
5. Oral Global Scale (**Appendix D**)
6. Painometer (POM) Assessment (
7. **Appendix** E)
8. Oral Health Impact Profile- OHIP-14 **(Appendix F)**
9. Hematology: Complete blood counts, with differential and platelet count
10. Chemistries: Electrolytes (including sodium, potassium, chloride, CO2, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, bilirubin, PT/INR and PTT, cortisol level and TBNK panel.
11. Research blood sample collection (18cc)
12. Five minute saliva sample, with and without paraffin stimulation
13. Clinical oral photo series
14. Hemoglobin A1C level
15. Short ACTH stimulation test (Per PI discretion at day 56 or day 70 depending on subject randomization group) if there is concern for endocrine side-effects)

3.5 Dose Modifications

No dose modifications are expected during this study.

3.6 Questionnaires

3.6.1 Oral Mucositis Rating Scale

Description. The OMRS was constructed through the careful selection of clinical descriptors of oral mucosal changes related to GVHD and also related to BMT[16]. The OMRS was developed

"…as a research tool for the comprehensive measurement of a broad range of oral tissue changes associated with cancer therapy" and "to develop an index for assessing acute oral mucositis after BMT[36]". Preliminary development of this scale was performed in studies of chemotherapy toxicities and cGVHD and use of the tool allowed "expedient, efficient, detailed, and reproducible classification of oral changes[36]". The OMRS was used by Schubert, Sullivan, Morton et al. (1984) with 60 patients, who were 180 to 500 days after ABMT, to determine if late oral abnormalities were associated with the presence of cGVHD. Oral manifestations found to be most strongly associated with cGVHD included atrophy and erythema or lichenoid lesions of the buccal and labial mucosa and oral pain[16].

The tool divides the oral cavity into seven distinct anatomic areas: lips; labial and buccal mucosa; tongue; floor of mouth; palate; and attached gingiva. Each site is further divided into upper and lower (lips and labial mucosa), right and left (buccal mucosa), dorsal, ventral, and lateral (tongue), and hard and soft (palate). Descriptive categories include atrophy, pseudomembrane, erythema, hyperkeratosis, lichenoid, ulceration, and edema. Erythema, atrophy, hyperkeratosis, lichenoid, and edema are rated on scales of 0 to 3 (0 = normal/no change, 1 = mild, 2 = moderate, and 3 = severe change). Ulceration and pseudomembrane are rated on scores based on estimated surface area involved (0 = none, 1 = ≥ 0 but ≤ 1cm^2, 2 = ≥ 1cm^2 but ≤ 2cm^2, and 3 = ≥ 2cm^2). The item pool consists of 91 items for 13 areas of the mouth that are assessed for several types of changes. The score is obtained by summing the scores of all items on the OMRS to yield a total possible score ranging from 0 to 273.

3.6.2 Painometer

Description. Pain will be self-assessed by subjects using a paper version of the Painometer , contains a visual analogue scale (VAS) to rate overall intensity of pain and a list of 14 sensory and 11 affective pain descriptors ranked by intensity values from 1 to 5 (POM-WDS)[37]. The POM is capable of capturing the multidimensionality of the pain experience. Patients are asked to look at the list of sensory and affective words (POM-WDS) and select sensory and affective words that describe their pain. The weighted scores assigned to the selected words are added together to obtain a pain intensity score for the sensory as well as for the affective components. The weights assigned to the words are derived from research involving people with various ethnic and educational backgrounds[37]. A vertical 10cm VAS (POM-VAS) is located on the POM with a centimeter scale allowing for overall pain intensity quantification. The POM-VAS is anchored with the words "no pain" located at the bottom of the scale and the words "worst possible pain" located at the top representing the extreme limits of pain. The patient is requested to circle a number indicating the amount of pain being experienced at the present time. The pain intensity score for the POM-VAS has a range of 1 to 10.

The affective and sensory pain scores are obtained by adding all of the respective intensity values. The range of possible sensory scores is from 0 to 48 and the range of possible affective scores is from 0 to 37. The sensory and affective scores may be added together to obtain the total pain intensity score for the POM-WDS, which may range from 0 to 85.

In a psychometric study that employed correlational and comparative designs, the test-retest reliability and the concurrent and construct validity of the POM-VAS and the POM-WDS were assessed in 279 patients with acute or chronic pain[37]. The following time intervals were used for

data collection using the POM: labor pain- admitted to labor and delivery, cervical dilation at 2 to 4 cm x 2 with a 10-minute interval, cervical dilation at 5 to 7 cm and again at 8 to 10 cm, immediately prior to epidural block, and another 30 minutes after epidural block; post-operative pain-4 hours after the patients were admitted to the recovery room after surgery, each time the patient complained of pain, and routinely every 4 hours, prior to and after pain medication was given; chronic pain in RA patients on two occasions with a 2-hour interval between each pain measurement. Relatively high correlations were found between initial and repeat intensity ratings for the POM-VAS ($r = .88$, $p < .001$). Test-retest reliability of the POM-WDS ranged from .68 ($p < .001$) to .73 ($p < .001$) in RA patients, from .80 ($p < .001$) to 0.84 ($p < .001$) in labor patients, and from .70 ($p < .001$) to .74 ($p < .001$) in postoperative patients. Concurrent validity of the POM-WDS was supported by correlations between the POM-WDS and the McGill Pain Questionnaire ($r = .069$, $p < .001$) and POM-VAS ($r = .85$, $p< .001$). Construct validity evidence was gathered for the POM by showing that pain scores decreased significantly for POM-WDS ($t = 5.53$, $p < .001$), and POM-VAS ($t = 6.18$, $p < .001$) after the patients had received pain medication. A correlation between the traditional paper-and-pencil VAS and the POM-VAS was reported to be 0.98 ($p < .001$).

A modified Gaston-Johansson Painometer Assessment Sheet will be used to record the following data regarding stomatitis-related acute oropharyngeal pain experienced at rest and with swallowing: intensity; sensory and affective descriptive words from the POM-WDS; duration (continuous or periodic).

3.6.3 Visual analogue scales for subject reported oral pain, oral sensitivity, and oral dryness

Subject reported oral pain, oral sensitivity, and oral dryness will be captured through use of a 0 to 10 visual analogue scale (VAS) anchored with the words “no pain” to “worst pain” (**Appendix C**). We will use this VAS to evaluate these symptoms over treatment.

3.6.4 Global Rating Scale (perception of changes in oral condition)

At the interim and final visits, we will assess patients’ perceptions of the changes in the oral condition on a 5 item scale (worsened greatly, worsened somewhat, stayed the same, improved somewhat, improved greatly). The data will be correlated with the results from the numerical scoring systems to assess internal validity (**Appendix D**).

3.6.5 Oral Health Impact Profile–14

Oral Health Impact Profile–14 (OHIP-14, Appendix F) is a 14 item questionnaire developed to assess the state of oral health as perceived by a patient [38,39]. Increased use of patient centered outcome measures has been advocated in the recent years. Patient centered outcome measures complement objective measures to provide a more complete picture of the impact of disease and treatment. OHIP-14 has been used in oral disease studies including oral lichen planus (a dermatological condition with manifestation similar to chronic oral GVHD). It has been shown to have high validity and reliability, and to be sensitive to treatment effects.

3.7 Study Calendar (see Appendix G)

3.7.1 Compliance

Subject adherence to the trial interventions will be estimated by measuring the volume of the remaining study medication at follow up appointments, study medication use diaries (**Appendix I**) and compliance with clinic visits. Correct use of the study medication will be demonstrated at the beginning of the study. Reinforcement such as periodic phone calls by the study nurses will be used to maximize compliance.

3.8 Duration of Follow- Up

Patients will be followed for 6 months total after discontinuing clobetasol oral rinse treatment every 3 months by telephone or in-person interview to assess duration of treatment response, recurrence of oral GVHD, survival and resolution of any side-effects. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Once there is resolution of adverse events, patients will be removed from study. Patients who become unavailable within 6 months of completing treatment will not be followed beyond the terminating event. Only adverse events at least possibly related to study treatment will be collected during the follow-up period.

3.9 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.9.1 Criteria for removal from protocol therapy

- Progressive oral cGVHD after 2 weeks of treatment with clobetasol: Patients will be unblinded at the time of GVHD progression and taken off treatment.
- Unacceptable toxicity: we do not expect significant adverse events associated with the study medication or procedures. In the event of unexpected toxicity attributable to the study drug (grade 2 or greater) patients will be taken off treatment.
- Change in the systemic immunosuppressive therapy while in the 2 week blinded phase
- Patient requests to stop therapy
- Investigator discretion

3.9.2 Off-Study Criteria

- Progressive oral cGVHD after 2 weeks of treatment with clobetasol: Patients will be unblinded at the time of GVHD progression and taken off study as defined in section **6.3.1**.
- Unacceptable toxicity: we do not expect significant adverse events associated with the study medication or procedures. In the event of unexpected toxicity attributable to the study drug (grade 2 or greater) patients will be taken off study.

- Patients unable to comply with study requirements will come off study. This includes ≥75% non-compliance with study oral rinse usage.
- Patients will come off study upon completion of follow-up Period (6 months after discontinuing clobetasol oral rinse treatment).
- Death
- Patient lost to follow up
- Patient withdrawal from follow-up period
- Change in the systemic immunosuppressive therapy while in the 2 week blinded phase
- PI decision to end this study

3.9.3 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov.

4 SUPPORTIVE CARE

Supportive care will be provided as specified in the primary transplant protocol and may include standard infection prophylaxis, anti-emetics, CMV surveillance at follow-up, topical care including topical analgesics, physical therapy, nutritional, and psychosocial support per NIH Blood & Marrow Consortium Supportive Care Guidelines (http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml). Anti-emetic therapy should not include dexamethasone or other corticosteroids.

4.1 CONCURRENT THERAPY

Topical corticosteroid treatment is associated with few potential complications. The most common is overgrowth of oral candidiasis. Many but not all patients with chronic GVHD are already taking antifungal prophylaxis such as oral fluconazole. Thus, to reduce incidence of oral candidiasis infection, patients will be asked to swish and spit once per day with nystatin (100,000u/ml) rinse, which is a standard preventative measure in high-risk patients. In case oral candidiasis develops, standard therapy according to NIH Consortium guidelines (http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml) with topical or systemic antifungals will be administered.

The use of additional topical or systemic immunosuppression is prohibited during the study period and should be avoided if possible during the cross-over/extension period. Other topical agents (oral or skin), are prohibited with the exception of topical viscous lidocaine supplied by the NIH pharmacy. However, the change in the systemic immunosuppressive medications will not be allowed while on the blinded phase of the study and will be avoided, if possible, on the

open label phase. If the absolute necessity develops to change or increase the systemic immunosuppressive therapy while in the blinded phase (e.g. for progressive GVHD in the organ sites other than oral cavity), patients will be taken off-study. Topical analgesic solution, available in NIH pharmacy (viscous lidocaine) will be permitted for control of oral discomfort. Other topical analgesics or mouthwashes will not be allowed. All interventions and medications dictated by the subject's primary transplant protocol and clinical necessity, including systemic analgesics, will be permitted. Subjects will keep daily records reflecting topical and systemic analgesic use (**Appendix I**). Factors that can potentially confound the results (such as change in systemic steroids and other immunosuppressants) will be taken into consideration in the final statistical analysis.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

5.1.1 Biologic studies

Adult patients will have no more than 10.5 ml/kg or 550 ml peripheral blood, whichever is smaller, drawn in 8-week study period for research studies. Children under 18 years of age will have no more than 9.5 ml/kg drawn in 8-week study period for research studies. These guidelines are according to The Clinical Center Policy and Communications Bulletin M95-9.

5.1.2 Immune Cell Kinetics in the Oral Tissues

The oral tissue sections will be examined by a pathologist to assess oral cGVHD status. Half of the biopsy will be formalin-fixed and sent to pathology for H&E staining. One quarter will be flash frozen for analysis of gene expression, and one quarter will be frozen in OCT media, and both quarters will be sent to Dr. Hakim's lab for storage (B10-Rm 12C216) until analysis. Immunohistochemical and PCR analysis will focus on characterization of cellular infiltrate, inflammatory cytokines, chemokines and protein mediators present at baseline and after clobetasol treatment.

5.1.2.1 Whole saliva samples will be examined for evidence of disease-related biomarkers associated with cGVHD and clobetasol treatment. Saliva will be collected in two 5-minute periods, one unstimulated and one stimulated with inert chewing (paraffin wax)[32]. The volume collected will be compared and used to indicate gland function[32]. Samples will be sent to will be sent to Dr. Hakim's lab for storage (B10-Rm 12C216) until analysis. *Samples are stored in locked freezers at -85°C.*

Blood samples will be used to measure cortisol levels and in a subset of samples, to determine blood levels of clobetasol during treatment with the mouth rinse formulation. Heparinized plasma and cells will be stored for potential analysis of inflammatory markers and cellularity associated with cGVHD and clobetasol treatment. Samples will be sent to will be sent to Dr. Hakim's lab for storage (B10-Rm 12C216) *in locked freezers at -85°C* until analysis.

One plasma sample (6 ml) will be sent to Dr. Figg's laboratory (B10-Rm 5A01) for storage *in locked freezers at -70°C* until LC-MS-MS analysis for clobetasol content. Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

5.1.3 Pharmacokinetic Studies

5.1.3.1 To determine if and how much clobetasol is absorbed through the oral mucosa in these cGVHD patients, blood levels of clobetasol (6 ml sample) will be monitored at baseline, 2- and 4-weeks of clobetasol rinse use. A random subset of half of the subjects (expected n=17) will be initially assessed for clobetasol plasma concentration. The determination of clobetasol concentrations in plasma samples, as well as the pharmacokinetic data analysis, will be performed by the Clinical Pharmacology Program (Dr. William Figg, Head - CPP, CCR, NCI). Samples will be analyzed using a validated LC-MS/MS method developed at the end of the trial. If this data indicates a positive correlation between plasma clobetasol level and the other study measures of adrenosuppression (ACTH stimulation test, morning cortisol levels), or if we see either unexpected clinical or surrogate responses, or wide variability in levels, the analysis will be extended to all study patients.

5.1.3.2 In a subset of consenting patients (up to n=10), the pharmacokinetics of clobetasol 0.05% mouth rinse will be assessed in a single session. After one two-minute oral rinse use, a venous blood sample will be collected in a 6 ml sodium heparin (green top) tube (BD Sodium Heparin 367878 or 367879) at x0, x15-45 and x90-120 minutes. The plasma clobetasol levels from these samples will be used to analyze the basic pharmacokinetics of clobetasol 0.5% oral suspension. Participation in this part of the study is optional, and a separate section has been included on the consent form to allow patients to elect participation or not. The first 10 patients who consent for the pharmacokinetics study will be selected for sampling.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.2.1 Storage/Tracking in the Preclinical Development and Clinical Monitoring Facility (PDCMF)

a) Samples will be ordered and tracked through the CRIS Screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside NIH without IRB notification and an executed MTA.

b) The *saliva, blood and tissue samples, collected for the purpose of research under IRB approved protocols of the Experimental Transplantation and Immunology Branch, will be stored and may be archived by the ETIB Preclinical Service Development and Clinical Monitoring Facility (PDCMF), with the exception of blood samples for clobetasol analysis, which will be stored separately by the* Clinical Pharmacology Program (CPP) until analysis. *All data associated with archived clinical research samples is entered into the ETIB PDCMF's Microsoft Excel databases on frozen cells and plasma. These databases are stored on the NCI group drive in the ETIB 'PRECLINSERVICE' folder.*

Access to this folder is limited to ETIB clinical staff, requiring individual login and password. All staff in the Preclinical Service laboratory received annually updated NIH/CIT training and maintain standards of computer security.

c) *The data recorded for each sample includes the patient ID, name, trial name/protocol number, date drawn, treatment cycle/post-transplant time point, cell source (e.g. peripheral blood, lymphapheresis, mobilized peripheral blood stem cells, marrow, oral biopsy) as well as box and freezer location. Patient demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI/ETIB clinical records or NCI C3D. All samples currently receive a unique bar code number, which is included in the PDCMF Stored Sample database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to patients without authorized access to the* PDCMF *database. All non-coded samples previously archived (prior to January 2007) are stripped of identifiers prior to distribution for any use other than as a primary objective of the protocol under which they were collected.*

d) *Samples are stored in freezers. All samples will be labeled solely with a bar code (which includes the date, and serially determined individual sample identifier). The key will be available to a restricted number of ETIB investigators and associate investigators on the protocol. Coded samples will be stored frozen at -20°, -80° or liquid nitrogen vapor phase to -180 C according to the stability requirements in a single location under the restricted control of the PDCM Facility of ETIB.*

e) *These freezers are located onsite at the Preclinical Service laboratory (12C216) (-85° freezer) or in ETIB common equipment space (CRC/3-3273).*

f) *Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol in order to be used (1) for research purposes associated with protocol objectives for which the samples were collected, or (2) for a new research activity following submission and IRB approval of a new protocol and consent, or (3) for use only as unlinked or coded samples under the OHSRP Exemption Form guidelines stipulating that the activity is exempt from IRB review. Unused samples must be returned to the PDCMF laboratory*

g) Samples, and associated data, will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to the PDCMF laboratory.

5.2.2 Protocol Completion/Sample Destruction in the PDCMF

a) Once research objectives for the protocol are achieved, researchers can request access to remaining samples, providing they have both approval of the Principal Investigator of the original protocol under which the samples or data were collected and either an IRB approved protocol and patient consent or the IRB Authorization Form stipulating that the activity is exempt from IRB review.

b) *The PDCMF staff will report to the Principal Investigators any destroyed samples, if samples become unsalvageable because of environmental factors (ex. broken freezer or*

lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher.

c) *The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.*

5.2.3 Sample Processing and Storage in the Blood Processing Core (BPC)

The determination of clobetasol concentrations in plasma samples, as well as the pharmacokinetic data analysis, will be performed by the Blood Processing Core (BPC). A venous blood sample will be collected in an 8ml SST tube to be processed for serum. Record the date and exact time of draw on the tube.

Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

The samples will be processed, barcoded, and stored in Dr. Figg's lab until requested by the investigator.

5.2.3.1 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.2.3.2 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services (American Type Culture Collection-ATCC) in

Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

6.1.1 Data Collection:

Data will be prospectively collected and entered into an NCI C3D Database using pre-designed CRFs. All patients must have signed an Informed Consent and have an on-study confirmation of eligibility form completed before entering on the study. Complete records will be maintained on each patient including the hospital chart with any supplementary information obtained from outside laboratories, radiology reports, or physician's records. These records will be the primary source documents that form the basis for the research record. The primary source documentation will assure the availability of the following: on-study information, including patient eligibility data and patient history; flow sheets, specialty forms for pathology, radiation, or surgery; and off-study summary sheet, including a final assessment by the treating physician.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Grade I AEs will only be recorded if they are deemed possibly, probably or definitely related to the study intervention.

6.1.2 Eligibility Checklist

To be completed at study entry and forwarded to protocol research nurse.

6.1.3 Protocol Deviations

Any protocol deviations should be directly reported to the PI or LAI.

6.2 ORAL GVHD SEVERITY SCALES

The primary endpoint will be evaluated using expanded oral GVHD severity scale (**Appendix A**)[33,34]. There is no standard definition of response in this field. The definitions we will use in this pilot study to grade the level of response to study intervention will be as follows:

- **Progression (PD):** defined as increase of 25% of initial score (rounded to the closest number) on the OMRS scale (**Appendix A**).
- **Partial Response (PR):** defined as decrease of 25% of initial score (rounded to the closest number) on the OMRS scale (**Appendix A**).
- **Complete Response (CR):** defined as score of 0 on the erythema and ulceration components of the OMRS scale (**Appendix A**).
- **Stable Disease (SD):** does not meet criteria for progression or response.

For the purpose of OMRS instrument evaluation validation, we will also use a simplified scale developed for assessment of cGVHD response in the oral cavity (**Appendix B**)[35]. Scoring will be performed by investigators trained in assessment of oral cavity lesions. As part of the evaluation of the scales, the results will be correlated with scores from symptom-oriented instruments and global scale.

6.3 RESPONSE CRITERIA

6.3.1 Response Criteria

The primary endpoint will be evaluated by using the OMRS (**Appendix A**). Secondary endpoints will be assessed using scales for oral discomfort and xerostomia, patient-reported global scale, and oral cavity specific quality of life questionnaire (OHIP-14).

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include

events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **6.1.**

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **7.2,** Error! Reference source not found. and **7.4**

An abnormal laboratory value will only be considered an AE, regardless of grade, if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subject.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB AND NCI CLINICAL DIRECTOR REPORTING

7.2.1 NCI-IRB and NCI Clinical Director Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and the NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations except drug compliance unless patients are less than 85% compliant with their medications.
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The following table will be used for reporting:

System Organ Class	CTCAE Term	Grade	# of Events since last CR	Total # of Events	Attribution to Research	Serious?	Unexpected?

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an Unanticipated Problem will need to be reported to the NCI IRB.

7.3 IND Sponsor Reporting Criteria

An investigator must immediately report to the sponsor, using the mandatory MedWatch form 3500a, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

- All Grade 5 (fatal) events (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- All other serious adverse events including deaths due to progressive disease must be reported within one business day

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

Events will be submitted to the Center for Cancer Research (CCR) at: CCRsafety@mail.nih.gov

7.4 FDA Reporting Criteria

7.4.1 IND Safety Reports to the FDA (Refer to 21 CFR 312.32)

The Sponsor will notify the FDA of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information using the MedWatch Form 3500a.

The Sponsor is also responsible for reporting any:

- suspected adverse reaction that is both serious and unexpected
- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

to the FDA and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendars days after receiving the request.

7.4.2 FDA Annual Reports (Refer to 21 CFR 312.33)

The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

7.5 DATA AND SAFETY MONITORING PLAN

Serious adverse events potentially attributable to the study medication or procedures will be reported to NCI IRB. If trends are noted and/or risks warrant it, accrual will be interrupted and/or the protocol and/or consent document will be amended accordingly.

7.5.1 Principal Investigator/Research Team

The clinical research team consisting of the PI, LAI, research nurse and data manager will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient, data acquisition, approve CRFs for data entry and address any other logistical issues pertinent to the integrity of the protocol implementation and data management.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The Principal Investigator and LAI will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.5.2 Sponsor Monitoring Plan

This trial will be monitored by personnel employed by Harris Technical Services on contract to the NCI, NIH. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

At least 25% of enrolled patients' will be randomly selected and monitored at least biannually or as needed, based on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 STATISTICAL CONSIDERATIONS

8.1 SUBJECT ACCRUAL

Subjects of both genders, from all racial and ethnic groups are eligible for this trial if they meet the criteria outlined in Section 2.1. To date, there is no information that suggests differences in drug metabolism or disease response among racial or ethnic groups or between the genders, indicating that results of the trial will be applicable to all groups. Efforts will be made to extend

the accrual to a representative population, but achievement of a fully representative subject population is unlikely in a pilot study with limited accrual.

8.2 STATISTICAL CONSIDERATIONS

The primary objective of this randomized pilot study is to determine if the use of clobetasol may result in improvement or stabilization in outcomes in patients with oral chronic GVHD. An important secondary objective is to preliminarily validate and explore the utility of the response measurement instruments.

Patients with oral cGVHD meeting the eligibility criteria will be separately randomized to either 1 month of clobetasol 0.05% oral rinse or placebo; there will not be separate accrual goals for each age group or type of underlying disease. The patients will be followed every 2 weeks for 1 month for their primary endpoint, and once 1 month after completion of study agents.

The primary endpoint will be the change in OMRS score (**Appendix A**) after 1 month of clobetasol 0.05% oral rinse compared to baseline. We will consider a 25% or larger decrease in the score to be clinically significant and a 'response' for the purpose of this study. As this is a pilot study, the association between this level of change and other scales will also be assessed to determine if this is a meaningful measure to use in future trials or if modification is warranted. Thus, this study will be a pilot for the determination of a meaningful response as well for determining if the agent tested may be beneficial.

After the first 2 weeks of clobetasol treatment, patients can be removed from study if oral disease progression is documented. Patients who are taken off study for oral disease progression will be counted as non-responders at the time of the final analysis. Patients taken off study for non-compliance, specifically ≥75% non-use of the oral rinse, will not be included in the data analysis

The patients enrolled on this study may be a very heterogeneous group with respect to prior treatments, extent of disease, etc. Patients taken off study for reasons unrelated to the primary outcome will be classified as non-responders and analyzed accordingly. The results will be interpreted in the context of a pilot study with potential limitations noted.

This study will aim to enroll a total of 34 evaluable patients randomized in a 1:1 fashion (17 per arm) to receive clobetasol rinse or placebo. The initial phase of the study will involve two weeks of either clobetasol rinse or placebo. At the end of the initial 2 weeks, patients receiving placebo will receive 28 days of clobetasol while those receiving clobetasol initially will receive an additional 14 days of clobetasol. Thus, each group will receive 28 days of clobetasol following either a 14 day placebo or immediately after randomization.

Patients will be randomized with a single stratification factor to try to ensure a balanced distribution among those getting placebo or not initially: being identified as having a high intensity of immunosuppression (2 or more agents/modalities ± prednisone≥0.5 mg/kg/day) vs. no or a lesser intensity of systemic immunosuppression according to the Intensity of Immunosuppression Scale [10]. This scale was developed using expert opinion, and has been preliminarily demonstrated to have predictive validity as measure of the intensity of systemic immunosuppression[10,40]. A low intensity regimen is defined as treatment with prednisone alone at a dose of less than 0.5 mg per kilogram per day. Moderately intense regimens include single agent prednisone at a dose greater than or equal to 0.5 mg per kilogram per day, and/or any other

single agent or modality. Regimens comprised of two or more agents or modalities (+/- prednisone greater than or equal to 0.5 mg per kilogram per day), are categorized as highly intensive systemic immunosuppression. When scoring the intensity of systemic immunosuppression, the use of topical agents is not captured.

The primary endpoint is the fraction of subjects who experience a 25% improvement in their OMRS compared to their own baseline. The fraction will be estimated with a two-tailed 95% confidence interval as the primary outcome. This will be done using all 34 patients together provided that the changes from baseline to day 28 for the two groups are sufficiently similar. A formal test will be performed assess their comparability. This will be determined conservatively, by obtaining the actual difference in the individual OMRS for each patient at baseline (day 0 for initial clobetasol and day 14 for those initially given placebo) vs. the value after day 28 of clobetasol and comparing those differences between the two randomized groups using a two-tailed Wilcoxon rank sum test. If the p-value for that comparison is >0.30, then the two groups will be considered sufficiently similar to allow pooling of the results and to report a combined fraction of patients who have a 'response' to 28 days of clobetasol. In this case 34 patients will be sufficient to allow the proportion of patients with a response of 75% or more to have a two-sided 95% confidence interval of +/- 15% or less, which will be considered sufficiently precise. Fractions of responses <75% would have slightly wider confidence interval widths.

An important secondary endpoint is to compare the changes from day 0 in the OMRS until day 14 between those who only receive placebo by that point vs. those who received clobetasol. This evaluation will be done both with respect to the fraction with a response by 2 weeks, as well as comparing the actual changes in OMRS from day 0 to day 14.

By enrolling 17 patients per arm, a 0.10 alpha level one-tailed Fisher's exact test will have 80% power to detect a difference between a potential 75% of patients having a 25% or greater decrease in severity score on the clobetasol arm and about half that amount, 35%, on the placebo arm. A one-tailed test is sufficient for this secondary objective in this study since we will not expect clobetasol to be associated with a lower fraction of patients with benefit compared to placebo and because this is intended to be a pilot study to determine if a potential trend of magnitudes anticipated, but not necessarily a statistically significant gain, may be detected. Should very promising results be obtained, then a subsequent trial could be conducted to build upon and further confirm the benefit noted.

A comparison of the actual levels of changes in the oral severity score between the arms will also be done using a Wilcoxon rank sum test as a secondary analysis. With 17 patients per arm, there is approximately 80% power to detect a difference between the arms in the changes from baseline to day 14 equal to one standard deviation of the change (effect size=1.0), using a two-tailed Wilcoxon rank sum test with a 0.05 significance level.

All patients will be placed on clobetasol for one month, whether following a two-week period with placebo or beginning at the time of randomization. In addition, comparisons between actual oral severity scores at the beginning of this period and one month later will be made using a paired t-test, or using a Wilcoxon signed rank test if the differences are not normally distributed ($p<0.05$ by Shapiro-Wilks test). These results will be evaluated separately according to the randomized treatment arm as well as overall if the changes in score according to the randomized assignments are similar ($p>0.30$ for Wilcoxon rank sum test comparing changes in scores

between the two arms over the one month clobetasol period). Although this would also be considered a secondary evaluation, there would be 82% power to identify a 0.75 standard deviation change to be significant with a two-tailed 0.05 alpha level paired t-test if all 17 patients are available within each arm for this comparison.

Patients will undergo oral mucosa biopsies at the beginning of the study, and many are expected to have biopsies at the end of 28 days of treatment. Although required, these biopsies may not be obtained on all patients, and the number of patients with paired data will determine the differences in immunologic parameters from the biopsies that can be detected. For example, if there were 20 patients with paired biopsy data and 5 immunologic parameters of interest, each one would have 93% power to detect a change with an effect size of 1.0, with a very conservative two-tailed 0.01 significance level, to account for multiple comparisons. Fewer than 20 patients with paired biopsies would reduce the power accordingly, but since this is a secondary objective, the results of these tests will be presented in the context of an exploratory study.

At a rate of 1 patient per 2 weeks accrual, approximately 16 to 20 months will be required to meet the accrual goal of 34 evaluable patients. To allow for a small number of inevaluable patients, the accrual ceiling will be set at 40 patients.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

No subjects will be excluded from participation based on gender, race or ethnicity. The study will be open to all subjects who satisfy the inclusion criteria and provide an informed consent to the protocol. From previous transplant protocol recruitment patterns at NIH we expect that over 80% of patients in this study will be adults over 18.

Recruitment: Subjects will be primarily recruited from NIH Clinical Center hematopoietic stem cell transplant clinics but could be referred from the outside institutions.

9.2 PARTICIPATION OF CHILDREN

This study will be limited to subjects aged 12 or older. Given the preliminary nature of the study and requirement for precise compliance with the instructions to minimize swallowing and systemic absorption of clobetasol, children < 15 who are less likely to comply will be excluded. In addition, due to the risk of swallowing, oral rinses such as topical fluorides are not recommended for young children.

9.3 PARTICIPATION OF NIH SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **9.5**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH

Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.4 Evaluation of Benefits and Risks/Discomforts

9.4.1 Related to Clobetasol

The side-effects of topical steroids are usually limited to Candida (yeast) infection. This is relatively uncommon in our patient population (<5%), easily treatable and does not require discontinuation of the treatment. Low levels of topical steroids are absorbed through the oral mucosa, but the exact rate is not known. While adrenal suppression is very rare with topically applied corticosteroids, it is physiologically possible. Cases of adrenal suppression following topically-applied steroid creams have been reported with long-term use on extensive body surface primarily in young children. In other reports, it was difficult to determine if there was adrenal suppression. Symptoms of adrenal suppression are non-specific and include fatigue, nausea and abdominal discomfort. Since these symptoms are extremely common in the general hospital population, routine monitoring in the context of this study is not indicated. In this study, blood pressure and serum cortisol will be monitored at every visit, and adrenal function will be assessed at baseline and at the end of the study. Given the short duration of this study, we do not expect significant side effects. We will use blood pressure, urine glucose, blood cortisol, and a baseline and repeat ACTH stimulation test at day 28 of clobetasol oral rinse use to monitor systemic steroid exposure. In the highly unlikely event of significant adrenal suppression as assessed by repeat ACTH stimulation test, Clinical Center Endocrinology Service will be consulted and subject will be placed on the standard oral hydrocortisone taper.

Topical steroid treatment may allow for local reactivation of viral infections, including but not limited to HSV. Patients will be monitored for oral HSV by PCR at the baseline and Day 28 visits.

9.4.2 Related to Blood Collection

Minor complications including bleeding, pain, and hematoma formation at the site of blood draws or infections may rarely occur.

9.4.3 Related to Tissue Biopsy

Oral mucosal punch biopsy is a minor surgical procedure that may be associated with temporary bleeding, hematoma at the site, local infection and postoperative discomfort. These risks are small (generally <5%) and transient.

9.4.4 Related to Pregnancy

Many post-transplant patients are not expected to become pregnant since ovarian failure is common in women after transplant. Women who are able to become pregnant will be expected to use an effective method of birth control. Although clobetasol will be applied topically in the

mouth in this study, there is no way of knowing how much medication will be absorbed into the bloodstream. Strong corticosteroids have caused birth defects in animals.

9.5 RISKS/BENEFITS ANALYSIS

9.5.1 For Adult Subjects

Post-transplant patients require monitoring for post procedure complications. Although this monitoring represents a minor increase over minimal risk monitoring is medically indicated. The risks of participating in this trial are limited to side-effects of clobetasol and the risks of standard diagnostic procedures (oral mucosal biopsy, plasma collection). Subjects may receive direct health benefits from participation in this protocol due to additional clinical monitoring such as thorough oral examination for oral GVHD. In addition, subjects on the active medication arm may receive direct benefit from treatment of oral GVHD.

This companion protocol to the primary transplant protocol requires the collection of an additional blood sample for research purposes only. Samples will be collected during sample collection procedures that are part of their routine standard therapy.

Therefore this study meets the DHHS Regulations 45 CFR § 46. criteria for "more than minimal risk to subjects with prospect of direct benefit to individual subjects".

9.5.2 For Pediatric Subjects

This study meets the DHHS Regulations as follows:

"The risk represents a minor increase over minimal risk". The risks of participating in this trial are limited to side-effects of clobetasol and the risks of standard diagnostic procedures (oral mucosal biopsy, plasma collection). Post-transplant patients require monitoring for post procedure complications. Although this represents a minor increase over minimal risk, said monitoring is medically indicated. This companion protocol to the primary transplant protocol requires the collection of additional blood samples for research purposes only. Oral biopsy is optional for the pediatric patients and will be performed only for clinical indications to rule out alternative diagnoses at enrollment and part of the tissue will be saved for research purposes

"The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations." Post-transplant patients who enroll in this protocol are familiar with blood collection and hospital procedures due to their frequent need for monitoring for their primary disease and for post-transplant complications. The monitoring that will be done is in line with the monitoring that would be done post-transplant.

"The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition." The generalizable knowledge would include the collection of information about the features of their post-transplant complication and the possible discovery of an effective treatment of oral GVHD for pediatric patients in the future.

Subjects may receive direct health benefits from participation in this protocol due to additional clinical monitoring such as thorough oral examination for oral GVHD. In addition, subjects on the active medication arm may receive direct benefit from prevention of oral GVHD.

"Adequate provisions are made for soliciting assent of the children and permission of the parent or guardian, as set forth in § 46.408." Only adult patients or pediatric patients via their guardians who satisfy the previously described inclusion/exclusion criteria and understand and have given informed consent and assent may enroll in the protocol. Some of the participants in this protocol will be children (less than 18 years of age). In these cases, full and informed consent must be obtained from the parent or the legal guardian and an assent obtained from the child. If the child does not wish to participate in the study, then enrollment of the child into the study is prohibited. Importantly, any subject who enrolls in the protocol has the option of withdrawing from the protocol at any time.

Therefore, the protocol meets 45 CFR § 46.406 criteria for "a minor increase over minimal risk to subjects with prospect of direct benefit to individual subjects".

9.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The investigational nature and research objectives of this trial, the procedure and its attendant risks and discomforts will be carefully explained to the patient or the patient's parents or guardian if he/she is a child, and a signed informed consent document will be obtained prior to entry onto the study. The potential subject will be educated regarding the nature of the condition, proposed intervention, and outcome measures. Study subjects will be informed that participation is entirely voluntary and that withdrawal from the study can be made at any time without penalty of benefits to which they may be entitled. Informed consent will be obtained by Dr. Jacqueline Mays, Dr. Steven Pavletic or an associate investigator of this protocol.

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Written assent will not be obtained from children as the study holds out the prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of the research. Verbal assent will be obtained as appropriate for children ages 12-17 and the parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

At any time during participation in the protocol that new information becomes available relating to risks, adverse events, or toxicities, this information will be provided orally or in writing to all enrolled or prospective patient participants. Documentation will be provided to the IRB and if necessary the informed consent amended to reflect relevant information.

The investigators are requesting a waiver from the IRB to allow only one parent to sign the informed consent to enter a child on the protocol. Because many patients must travel to the NIH from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial hardship for many families. When guardianship status of the child is uncertain, a social worker will be asked to investigate and, if necessary, seek documentation of custody status.

In situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH, the other parent's consent can be obtained by telephone via the procedure described in section **9.6.1**.

9.6.1 Telephone re-consent procedure

Re-consent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

9.6.2 Informed consent of Spanish speaking subjects

We anticipate the enrollment of Spanish speaking research participants into our study. The IRB approved full consent document will be translated into that language in accordance with the Clinical MAS Policy M77-2.

9.6.3 Short form consent process for other non-English speaking patients

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

10 PHARMACEUTICAL INFORMATION

10.1 CLOBETASOL ORAL RINSE

Other: Clobetatasol propionate, Temovate

Classification: Corticosteroid

Action: Anti-inflammatory and Immunosuppressive. Clobetasol is a high-potency corticosteroid with mainly glucocorticoid activity;

Supply / Availability: Commercially available in powder form (Spectrum Chemicals). The commercial supply will be prepared as a 0.05% oral rinse and labeled as study drug specific to this protocol by the Pharmaceutical Development Section of the NIH CC Pharmacy.

Product description: Clobetasol oral rinse 0.05% (500mcg/mL) is a clear, colorless solution

Active Ingredient: clobetasol propionate

Preparation: The commercially available clobetasol powder will be dissolved in the diluent, hydroxypropylated cyclodextrin in water, then methylparaben, propylparaben and ascorbic acid will be added. Oral rinse will be repackaged in an 8 ounce amber bottle and relabeled as study drug for the purposes of this study and to allow blinding of the patient, clinical staff, and investigators.

Storage: Store at room temperature (20º to 25ºC (68º to 77ºF) (see USP controlled room temperature.

Administration: Rinse oral cavity for 2 minutes and spit out. Use 3 times daily: after breakfast, lunch and before bedtime. DO NOT SWALLOW. Do not eat or drink for 30 minutes after use.

Dose: 10 mL (5mg)

Toxicities: see section **6.4**

10.2 STUDY PLACEBO ORAL RINSE

Supply: The placebo oral rinse will be prepared by the Pharmaceutical Development Section of the NIH Clinical Center Pharmacy and labeled as study supply for purposes of this study and to allow blinding of patients, clinical staff, and investigators.

Product Description: The placebo oral rinse contains the following ingredients: hydroxypropylated cyclodextrin, methylparaben, propylparaben, ascorbic acid, quinine, and water for injection.

Storage: Store at room temperature (20º to 25ºC (68º to 77ºF) (see USP controlled room temperature.

Administration: Rinse oral cavity for 2 minutes and spit out. Use 3 times daily: after breakfast, lunch and before bedtime. DO NOT SWALLOW. Do not eat or drink for 30 minutes after use.

Dose: 10 mL

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12 APPENDICES

APPENDIX A: ORAL MUCOSITIS RATING SCALE (OMRS)

INSTRUCTIONS: Assess each indicated oral cavity location for the stated clinical observation and write in the number corresponding to the rating.

	LIPS		LABIAL MUCOSA		BUCCAL MUCOSA	
	Lower	Upper	Lower	Upper	Right	Left
Atrophy						
Pseudomembrane						
Erythema						
Hyperkeratosis						
Lichenoid						
Ulceration						
Edema/Cellulitis						

	TONGUE			FLOOR OF MOUTH	PALATE		GINGIVA
	Dorsal	Lateral	Ventral		Hard	Soft	
Atrophy							
Pseudomembrane							
Erythema							
Hyperkeratosis							
Lichenoid							
Ulceration							
Edema/Cellulitis							

Total OMRS Score: _____ (range: 0 – 273; sum all items)

Rating Criteria

Change is rated from normal

Atrophy, erythema, hyperkeratosis, lichenoid , and edema

0 = Normal/No change
1 = Mild change
2 = Moderate change
3 = Severe change

Ulceration and Pseudomembrane

0 = None
1 = > 0 but ≤ 1cm^2
2 = 1 cm^2 but ≤ 2 cm^2
3 = > 2cm^2

If any area cannot be assessed, circle one of the following:

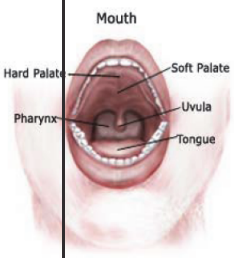
04 = Unable to visualize/assess due to severity
05 = Unable to assess because patient is sedated
06 = Unable to assess because patient is disoriented
07 = Unable to assess because patient is comatose
08 = Unable to assess because patient is unwilling or unable to cooperate
09 = Unable to assess because patient is not available. Explain: _____
_____
10 = Other. Explain: _____
99 = Missing

Check (√) type of light source used to visualize the oral cavity:
____ (1) Otoscope ___ (2) Dental Light _____ (3) Other

_____ (1) Oral water rinse used
_____ (2) Local anesthetic used

APPENDIX B: ORAL CGVHD CLINICAL SCORING INSTRUMENT

Mouth



Mucosal change	No evidence of cGVHD		Mild		Moderate		Severe	
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Hyperkeratotic changes(<25%)	1	Hyperkeratotic changes(25-50%)	2	Hyperkeratotic changes (>50%)	3
Ulcers	None	0	None	0	Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
Mucoceles*	None	0	1-5 mucoceles	1	6-10 scattered mucoceles	2	Over 10 mucoceles	3
			*Mucoceles scored for lower labial and soft palate only				**Total score for all mucosal changes**	

APPENDIX C: NUMERIC RATING SCALES (0-10) FOR ORAL PAIN, SENSITIVITY, AND DRYNESS

ORAL PAIN

On a 0 to 10 scale, how PAINFUL is your mouth now? Please circle the number.

0 1 2 3 4 5 6 7 8 9 10

No pain Worst pain

ORAL SENSITIVITY

On a 0 to 10 scale, how SENSITIVE is your mouth now? Please circle the number.

0 1 2 3 4 5 6 7 8 9 10

No sensitivity Worst sensitivity

ORAL DRYNESS

On a 0 to 10 scale, how DRY is your mouth NOW? Please circle the number.

0 1 2 3 4 5 6 7 8 9 10

No dryness Worst dryness

APPENDIX D: GLOBAL SCALE

Compared to TWO WEEKS ago, what is the overall condition of your mouth? Please circle.

Much worse A little worse Same A little better Much better

APPENDIX E: PAINOMETER (POM) ASSESSMENT SHEET

Baseline **Date: _____/_____/_____** **Time: _____** **Subject Study Number: _____**

I INSTRUCTIONS: Ask the participant to choose words from the Sensory pain intensity list and the Affective pain intensity list below to describe present oral pain- Circle the chosen letter/word and number/word from the lists.

SENSORY	AFFECTIVE
A Cramping	1. Nagging
B. Dull	2. Agonizing
C. Splitting	3. Annoying
D. Burning	4. Troublesome
E. Sore	5. Killing
F. Shooting	6. Tiring
G. Radiating	7. Unbearable
H. Hurting	8. Sickening
I. Crushing	9. Terrifying
J. Aching	10. Miserable
K. Stabbing	11. Torturing
L. Sharp	
M. Tearing	
N. Pressing	

II. INSTRUCTIONS: Ask the participant to choose the word which describes the duration of oral pain and check the response:

Continuous _____ Periodic (Comes and goes) _____

III. INSTRUCTIONS: Ask the participant to choose words from the Sensory pain intensity list and the Affective pain intensity list below to describe present oral pain with swallowing
Circle the letters/numbers and words chosen from the lists.

SENSORY	AFFECTIVE
A. Cramping	1. Nagging
B. Dull	2. Agonizing
C. Splitting	3. Annoying
D. Burning	4. Troublesome
E. Sore	5. Killing
F. Shooting	6. Tiring
G. Radiating	7. Unbearable
H. Hurting	8. Sickening
I. Crushing	9. Terrifying
J. Aching	10. Miserable
K. Stabbing	11. Torturing
L. Sharp	
M. Tearing	
N. Pressing	

IV. INSTRUCTIONS: Ask the participant to choose the word which describes the duration of oral pain with swallowing and (') the response

Continuous _____ Periodic (Comes and goes) _____

Scoring of Painometer (POM) Assessment Sheet

Weighted scores for the Painometer sensory word descriptors are:

A. Cramping = 4
B. Dull = 1
C. Splitting = 5
D. Burning = 4
E. Sore = 1
F. Shooting = 5
G. Radiating = 3
H. Hurting = 2
I. Crushing = 4
J. Aching = 3
K. Stabbing = 5
L. Sharp = 5
M. Tearing = 5
N. Pressing = 2

Weighted scores for the Painometer affective word descriptors are:

1. Nagging = 1
2. Agonizing = 4
3. Annoying = 1
4. Troublesome = 2
5. Killing = 5
6. Tiring = 3
7. Unbearable = 5
8. Sickening = 4
9. Terrifying = 5
10. Miserable = 3
11. Torturing = 5

Total score is calculated by simple summation of individual weighted scores.

APPENDIX F: ORAL HEALTH IMPACT PROFILE (OHIP-14) [38]

Date: ____/____/____ Timepoint: _____ LIP print name: Jacqueline Mays LIP Signature:_____

#	Because of problems with your teeth, denture or mouth have you…	Never (0)	Hardly ever (1)	Occasionally (2)	Often (3)	Very Often (4)
1	Had trouble pronouncing words					
2	Felt sense of taste has worsened					
3	Had painful aching in the mouth					
4	Found it uncomfortable to eat any foods					
5	Have been self-conscious					
6	Felt tense					
7	Had an unsatisfactory diet					
8	Had to interrupt meals					
9	Found it difficult to relax					
10	Have been a bit embarrassed					
11	Have been irritable with other people					
12	Had difficulty doing usual jobs					
13	Felt life in general was less satisfying					
14	Have been totally unable to function					

Total _____

APPENDIX G: SCHEDULE OF EVALUATIONS AND EVENTS

Patients Randomized to Clobetasol Oral Rinse Schedule:

Patient Evaluations and Events	**Screening and Baseline (Day -7 to 0)***	**Day 0 ***	**Interim Evaluation (Day 14) *g**	**End of Intervention (Day 28) ***	**Follow-up (Day 56) *** **(or end of treatment visit)**	**Follow up (3 months and 6 months post treatment)#**
History and Physical Exam[t]	X[t]		X[t]	X[t]	X[t]	X[t]
NIH Advanced Directives Form						
cGVHD NIH Organ Staging	X				X	
Clinical Photographs	X		X	X	X	
Urine pregnancy test	X					
Informed Consent	X					
Randomization	X					
CBC, Acute care, mineral and liver panel & LDH, TBNK	X		X	X	X	
Serum Cortisol Level	X		X	X	X	
Research Saliva and Plasma Collection	X		X	X	X	
OMRS	X		X	X	X	

Patient Evaluations and Events	**Screening and Baseline (Day -7 to 0)***	**Day 0 ***	**Interim Evaluation (Day 14) *g**	**End of Intervention (Day 28) ***	**Follow-up (Day 56) *** **(or end of treatment visit)**	**Follow up (3 months and 6 months post treatment)#**
Oral cGVHD Clinical Scoring	X		X	X	X	
Oral HSV by PCR	X			X		
Oral Pain, Sensitivity, Dryness Scales	X		X	X	X	
Global Scale			X	X	X	
POM	X		X	X	X	
OHIP-14 (Oral QOL)	X		X	X	X	
Biopsy/Tissue Collection	X			X[t]		
ACTH Stimulation Test	X			X	X[p]	
Adrenocorticotropic Hormone blood level	X			X	X	
Hemoglobin A1C level	X	X	X	X	X	
Compliance Evaluation			X	X		
Monitoring for Adverse Events			X	X	X	X
Start of intervention		X				
Completion of the intervention				X		

[*] ± 2 days

[t] Optional

[p] Per PI discretion (at day 56 or day 70 visit depending on subject randomization group) if there is concern for endocrine side-effects)

[#] This follow up can be done in person or via telephone call as per section **3.8**[g] Patients initially randomized to 2 weeks of placebo will have two Day 14 Interim Evaluation visits, one at unblinding and one after 14 days of clobetasol therapy.

[h] As indicated in section **9.5**, all subjects ≥ age 18 will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

APPENDIX H: DATA COLLECTION ELEMENTS REQUIRED BY PROTOCOL

All of the following elements will be recorded in the C3D database.

Patient Enrollment

Recipient

- Date of birth, age, gender, race, ethnicity
- Height
- Weight
- Karnofsky Performance Status
- Date of original diagnosis of the underlying disease (month/year)
- Diagnosis for which transplant was performed
- Date and type of transplant
- Conditioning regimen
- Acute GVHD yes/no
- Chronic GVHD date of diagnosis
- Chronic GVHD classification (late, overlap, classic)
- Prior systemic therapy for cGVHD
- Prior oral therapy for cGVHD
- Date of Informed Consent signature, consent version and date of registration
- Optional Baseline History/Physical
- Baseline Symptoms
- Intensity of current immunosuppression: None, Mild (single agent prednisone $\leq$0.5 mg/kg/day), Moderate (prednisone $\geq$0.5 mg/kg/day and or any single agent/modality), High (2 or more agents/modalities $\pm$prednisone $\geq$0.5 mg/kg/day)
- Clinician's impression of activity: Inactive, off systemic therapy or topical immunosuppression; Inactive, on systemic therapy or topical immunosuppression; Active, irrespective of the level of current therapy; Highly Active, irrespective of the level of current therapy
- Findings of consultations done at screening

Donor

- Age at transplant
- Relationship, gender
- Degree and type of HLA match (allele or serologic)
- CMV status

Study Drug administration and response for each course of therapy given

- Dates study rinse given
- Actual dose given
- Response assessment (OMRS score) for each visit

Laboratory and Diagnostic Test Data

- All Clinical laboratory and diagnostic test results done at screening except diagnostic tests which are not specified in the protocol, and if the results are not needed to document the start or end of an adverse event that requires reporting.
- All tests done to document resolution of adverse events
- Serologies-CMV and HSV
- Volume of stimulated and unstimulated saliva at each visit.

Adverse Events

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems

Concomitant Measures

- Baseline immunosuppressive medications
- Other therapy for recorded adverse events

Off study

- Date and reason for off study
- Date and cause of death
- Autopsy findings

APPENDIX I: TOPICAL CLOBETASOL 0.05% ORAL RINSE FOR ORAL CHRONIC GRAFT-VERSUS-HOST DISEASE PATIENT DIARY

INSTRUCTIONS: Rinse with the study medication THREE times a day for 2 minutes and spit out. Do not eat, drink or brush your teeth for at least 30 minutes after study medication use.

Rinse with the nystatin suspension ONE time a day for at least 30 seconds after your evening meal. Do not eat, drink or brush your teeth for at least 10 minutes after nystatin use.

You can use painkiller rinse (viscous lidocaine) as needed to relieve oral discomfort. Do not use the painkiller rinse at least 30 minutes before and after using the study rinse or nystatin. Do not use any other mouthwashes, rinses or oral hygiene products except toothpaste.

Record the level of oral pain and oral dryness for the day at its WORST using a number from 0 (no pain/dryness) to 10 (the worst possible pain/dryness).

Day of the week	Date	Time Write down the time you use a dose of study rinse and circle AM or PM. (Remember that you are to use the rinse 3 times per day)		Mouth Pain Rating Rate your pain with the first daily rinse by circling the number on the 0 to 10 pain scale. Zero (0) is no pain and ten (10) is the worst pain	Mouth Dryness Rating Rate your dryness before the first daily rinse by circling the number on the 0 to 10 pain scale. Zero (0) is no dryness and ten (10) is the worst dryness	Medications for Pain List any medications you have taken for **pain in your mouth** in the past 24hrs	Side Effects List any side effects that you have experienced in the past 24hrs	Comments Include any additional information such as why you missed/skipped a dose of study rinse
		Dose 1	AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2	AM/PM					
		Nystatin	PM					
		Dose 3	AM/PM					
		Dose 1	AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2	AM/PM					
		Nystatin	PM					
		Dose 3	AM/PM					
		Dose 1	AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2	AM/PM					
		Nystatin	PM					
		Dose 3	AM/PM					
		Dose 1	AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2	AM/PM					
		Nystatin	PM					
		Dose 3	AM/PM					
		Dose 1	AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2	AM/PM					
		Nystatin	PM					
		Dose 3	AM/PM					
		Dose 1	AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2	AM/PM					
		Nystatin	PM					
		Dose 3	AM/PM					
		Dose 1	AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2	AM/PM					
		Nystatin	PM					
		Dose 3	AM/PM					

Patient Signature:________________________ Date:_________

APPENDIX J: SPANISH LANGUAGE TRANSLATIONS OF THE PATIENT-REPORTED OUTCOME FORMS

Painometer (POM) Assessment Sheet

Date: ____/____/____ Time: _____ Timepoint: _____ LIP: Jacqueline Mays LIP **Signature:**_____

I INSTRUCCIONES: Pídale al participante que elija palabras de la lista de intensidad del dolor Sensorial tanto como de la lista de intensidad de dolor Afectivo a continuación, para describir el dolor oral en estos momentos. Haga un círculo alrededor de la letra y palabra y del número y palabra de las listas a continuación.

SENSORIAL	AFECTIVO
A Calambre	1. Irritante
B. Leve	2. Agobiante
C. Enloquecedor	3. Fastidioso
D. Ardor	4. Molestoso
E. Adolorido	5. Mortal
F. Punzante	6. Fatigoso
G. Que irradia	7. Insoportable
H. Que duele	8. Deprimente
I. Triturante	9. Espantoso
J. Resentido	10. Miserable
K. Como puñaladas	11. Torturante
O. Agudo	
P. Desgarrante	
Q. Insistente	

II. INSTRUCCIONES: Pídale al participante que elija la palabra que describe la duración del dolor oral y marque la respuesta:

Continuo _____ Periódico (Se viene y se va) _

III. INSTRUCCIONES: Pídale al participante que elija palabras del listado de intensidad del dolor Sensorial y del dolor Afectivo a continuación, para describir el dolor oral al deglutir. Marque con un círculo las letras/números y los números/palabras de estas listas.

SENSORIAL	AFECTIVO
A Calambre	1. Irritante
B. Leve	2. Agobiante
C. Enloquecedor	3. Fastidioso
D. Ardor	4. Molestoso
E. Adolorido	5. Mortal
F. Punzante	6. Fatigoso
G. Que irradia	7. Insoportable

H. Que duele
I. Triturante
J. Resentido
K. Como puñaladas
L. Agudo
M. Desgarrante
N. Insistente
8. Deprimente
9. Espantoso
10. Miserable
11. Torturante

IV. INSTRUCCIONES: Pídale al participante que elija la palabra que describa la duración del dolor oral al deglutir y la respuesta.

Continuo _____ Periódico (Se viene y se va) _

Global Scale-0 to 10 Scales

Numeric Rating Scales (0-10) for Oral Pain, Sensitivity, and Dryness

DOLOR ORAL

En una escala del 0 al 10, ¿qué tanto DOLOR siente en su boca en este momento? Por favor marque el número adecuado con un círculo.

0 1 2 3 4 5 6 7 8 9 10

No siento dolor El peor que he sentido

SENSIBILIDAD ORAL

En una escala del 0 al 10, ¿qué tan SENSIBLE siente su boca en este momento? Por favor marque el número adecuado con un círculo.

0 1 2 3 4 5 6 7 8 9 10

No sufro de sensibilidad La peor sensibilidad que he sentido

RESEQUEDAD ORAL

En una escala del 0 al 10, ¿qué tan SECA siente su boca EN ESTE MOMENTO? Por favor marque el número adecuado con un círculo.

0 1 2 3 4 5 6 7 8 9 10

No siento resequedad La peor resequedad que he sentido

Escala Global

Si compara la condición actual de su boca, con la condición en la que estaba HACE DOS SEMANAS, ¿en que condición general esta su boca? Por favor, marque con un círculo.

Mucho peor Un poco peor Igual Un poco mejor Mucho mejor

LIP Print Name: Jacqueline Mays LIP Signature:_____

Date of Evaluation:_____

Timepoint:_____

Appendix K: Oral Health Impact Profile (OHIP-14)

Date: ____/____/____ Timepoint: _____ LIP print name: Jacqueline Mays LIP Signature:_____

#	**Ha tenido los siguientes problemas, debido a dificultades con su boca, sus dientes o dientes postizos:**	**Nunca (0)**	**Casi nunca (1)**	**Ocasional-mente (2)**	**Frecuente-mente (3)**	**Muy frecuen-te (4)**
1	¿Ha tenido dificultad al pronunciar palabras?					

2	¿Se ha empeorado el sentido del gusto ha empeorado?					
3	¿Ha estado adolorida su boca?					
4	¿Se siente incómodo al comer?					
5	¿Se siente muy consciente de sí mismo?					
6	¿Se siente tenso/a?					
7	¿Ha sido insatisfactoria su dieta?					
8	¿Ha tenido que interrumpir tiempos de comida?					
9	¿Se da cuenta que le es muy difícil relajarse?					
10	¿Se siente un poco avergonzado/a?					
11	¿Se ha sentido muy irritable hacia otras personas?					
12	¿Ha tenido dificultad haciendo cosas que usualmente ha hecho sin dificultad?					
13	¿Se siente menos satisfecho/a con su vida en términos generales?					
14	No ha podido funcionar del todo.					

Total _____

INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0068 PRINCIPAL INVESTIGATOR: Steven Pavletic, MD

STUDY TITLE: A Randomized Double-Blind Pilot Study of Topical Clobetasol 0.05% Oral Rinse for Oral Chronic Graft Versus-Host Disease

Continuing Review Approved by the IRB on 08/22/16
Amendment Approved by the IRB on 02/14/17 (H) Date posted to web: 03/01/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Description of Research Study

You are being invited to participate in a research study testing whether a drug called clobetasol is effective in oral chronic graft versus host disease (oral cGVHD) - a common complication of stem cell transplantation that occurs in up to 60% of transplant patients. GVHD occurs when, after a transplant, the donor's cells attack and damage the recipient's tissues.

Clobetasol is a corticosteroid, a class of drugs that are commonly used to treat inflammation. Corticosteroids are known to affect the cells of immune system and may help to "turn down" the activity of the donor cells. Corticosteroids taken by mouth or injected have been proven to be effective for the treatment of cGVHD however they are associated with many side effects such as high blood pressure and diabetes. Topically applied (used on the surface, like creams or rinses) corticosteroids have relatively few side–effects but their role in the treatment of oral GVHD has not been well studied. Therefore, this study will investigate whether clobetasol rinse can decrease the severity of oral cGVHD in patients after their transplant and its effects on the cells of the lining of the mouth.

You can participate in this study if you:

- have signs of oral GVHD,
- are not allergic to clobetasol,
- are 12 years of age and older,
- did not have any changes in systemic (taken by mouth or injected, i.e. pills or shots) immunosuppressive therapy in the two preceding weeks
- are able to rinse with the study medication by mouth,
- are able to come back to NIH for follow-up appointments, and
- are not pregnant and are using a birth control method that meets the requirements of this study

What Are the Treatments and What is the Course of the Study?

Investigational Treatment

If you decide to participate, you will be first randomly (like the flip of a coin) assigned to receive either (1) clobetasol rinse or (2) placebo (an oral rinse that looks and tastes like the clobetasol rinse but has not active medication). You and the research team will not have a choice of which medication you receive in the first 2 weeks of the study. Likewise, neither you nor the investigators will know which medications you are taking until completion of the first 2 weeks of the study. However, in case of emergency, the information regarding which drug you are using will be available from the NIH pharmacy.

After the first 2 weeks, you will start using clobetasol rinse for another 2 or 4 weeks depending on whether you were originally assigned to placebo or clobetasol. That way every patient on the study will receive clobetasol for a total of 4 weeks.

You will rinse your mouth out with the study oral rinse 3 times a day after meals every day. You will take 10 ml of the oral rinse using the measuring cup, put it in your mouth and swish it around for 2 minutes and spit out the oral rinse into the sink. DO NOT SWALLOW THE RINSE! The oral rinse that we are using is not intended for internal use and we want to limit the

action of the drug to the mouth and decrease the effects of the steroid on the rest of the body. Please do not eat or drink for 30 minutes after use.

Should you swallow the rinse, please contact Dr. Pavletic.

Additional Treatment Period

After you have completed four weeks of clobetasol treatment, it may be possible for you to be treated with the clobetasol for up to an additional four weeks. You would need to restart the clobetasol within 90 days of your last dose of clobetasol in order for this to occur, and a follow-up exam at NIH must be done for you to qualify for re-treatment.

Non-Investigational Treatments

You will be given a painkiller rinse (viscous lidocaine, numbing rinse) that you can use to relieve the discomfort in the mouth. You can apply it to the affected areas in the mouth up to 3 times a day before eating but at least 30 minutes apart from the study rinse.

A potential anticipated side-effect of local corticosteroid treatment is yeast infection in the mouth. To prevent this, you will be asked to rinse once per day with an anti-fungal medication, nystatin suspension.

You will continue to take all medications that are prescribed as part of your post transplant care. However, no changes in the immunosuppressive medications will be allowed for the first two weeks of the study. The immunosuppressive medications include but are not limited to cyclosporine, tacrolimus (Prograf), mycophenolate (MMF, Cellcept) and prednisone. Changes in immunosuppressive medications will be allowed after the first 2 weeks of the study if necessary to control GVHD in sites other than the mouth. We will ask you about the use systemic steroids, immunosuppressants and pain medication use at the time of each evaluation.

Study Evaluations

Evaluations done to assess study eligibility

To ensure your safety, you will undergo a series of brief assessments to determine if you are a good candidate for protocol participation. These tests and procedures will be done under a separate screening protocol and will be fully described in that consent document.

History, oral exam, physical: We will perform a brief oral examination and explain the protocol procedures. We may also perform a physical exam and take your medical history.

Medication review: Some medications might reduce the effectiveness or increase the side effects of clobetasol and clobetasol may increase the side effects of or lessen the effectiveness of some medications. Therefore, we will need to review over-the counter-medications, health food supplements, and prescription medication that you are taking before you take part in this study.

Pregnancy testing: Women of childbearing age will have a pregnancy test, which must be negative before they take part in the study.

Evaluations and procedures done after consent but before starting study medication

Oral Exam: We will do a complete soft tissue exam of your mouth.

Oral photographs: We will take photographs of your mouth and the surrounding area.

Biopsy of Your Mouth: At the first visit, we will take one small piece of tissue (about 4mm across) from the inside of your cheek. We will numb the inside of your cheek and use a punch (size of a pencil eraser tip) to remove the tissue. This is a minor procedure with few side effects usually limited to some post-operative discomfort for about a day. Half of the tissue will be saved for research, and the other will be sent to the lab to be reviewed by a pathologist. Part of this tissue will be used for pathological examination to confirm your condition. Another part will be used in our lab to study factors that are associated with the development of GVHD in the mouth. This biopsy is required as part of this research study. After the initial biopsy, if you decide not to have further biopsies, you will still receive study drugs and have other tests as part of this study. You will be asked to sign a separate consent form for each biopsy procedure. Children will only have oral biopsy done if it is needed for medical reasons.

Saliva Tests: Saliva will be collected by spitting in the tube for 5 minutes. This will be done two times at each appointment: once while chewing a small piece of paraffin wax and once without wax. This is a simple procedure that does not have any risks or discomforts. We will use saliva samples to measure your salivary gland function and to study in our laboratory factors that may be associated with the development of GVHD including the types of protein in the mouth.

Blood sample collection: We will draw blood from your arm by a trained person. We will ask you sit or lie down when we take your blood. We will tie a large rubber band around the upper arm, and then we will cleanse the area on your arm with an alcohol swab, where we intend to take the blood. At the site we cleansed, we will place a tiny needle under the skin into a vein in your arm and we will fill-up 5 of tubes or less the size of your pinky with your blood. Once we are done getting the blood, we will remove the tiny need and cover the site with a band aid.

Questionnaires: You will be asked to fill out questionnaires which will measure your quality of life, your mouth pain and mouth dryness.

ACTH Stimulation Test: This test is used to evaluate the how well your adrenal glands work. Adrenal glands are normally responsible for production of steroids in the body. Sometimes, if steroids are taken for a long time, the adrenal glands react by decreasing their own production. This is called "adrenal suppression" and may result in decreased blood pressure and decreased ability to fight infection and cope with stress of trauma or surgery. Although, this generally happens when corticosteroids are given orally it is possible that in some cases corticosteroid from a rinse is taken by the body through oral lining. It is unknown how much effect this could have on the adrenal glands; therefore, we would like to evaluate your adrenal gland function by performing ACTH stimulation test.

This test is performed in the morning at 8 o'clock. You will have to be in a bed and we will give you an intravenous injection of a drug called "ACTH" or "cosynthropin" which is version of a

hormone normally produced by your pituitary gland. We will draw blood before and at 30 and 60 minutes after the injection to measure your cortisol levels. Children will only have an ACTH stimulation test done if it is needed for medical reasons.

Evaluations and procedures done during study drug administration (Day 0 to 4-6 weeks)

We ask that you return to the Clinical Center 2 weeks after starting study drug at which time baseline assessments will be repeated.

Oral exam: at each visit

Oral photographs: at each visit

Oral biopsy: at the 4-6 weeks visit (at the end of the treatment phase of the study). We will obtain an additional small (4 mm) punch biopsy sample for research purposes only. The biopsy will be taken from inside of your cheek from an area of the cheek near the healed spot from the first biopsy. This will be used to compare to the sample obtained before treatment was started. The biopsy to be performed is exclusively for research purposes and will not benefit you. It may help other people in the future.

Saliva samples: at each visit

Review of medications: at each visit

Study drug compliance: at each visit we ask that you return the medication diary and any unused medication so we can measure how much study drug you have taken.

Blood collection: at each visit

Questionnaires: You will be asked to assess your level of dry mouth and oral pain at each visit and complete one quality of life assessment at the 1-month visit only.

ACTH Stimulation Test: at the end of the investigational treatment or if you are taken off-study. This may be repeated at your final study visit, 8 weeks after starting active clobetasol rinse, if your doctors are concerned about adrenal suppression.

Follow-Up Evaluations

We will contact you every 3 months after you stop using clobetasol oral rinse for 6 months to assess duration of treatment response, recurrence of oral GVHD, and resolution of any side-effects you may have experienced. You will be contacted by a study team member by telephone or in person if you are already at the NIH for other treatment at a follow-up time point.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

Related to Clobetasol:

Corticosteroids can be taken either internally as a pill or injections or topically as a cream or ointment. In this study the corticosteroid is used topically which hopefully will avoid many of the unwanted side-effects that are associated with the drug which include:

Likely

- Yeast infection (thrush). Short-term topical corticosteroid treatment is associated with few potential complications. The most common is yeast overgrowth. This is easily treated and does not require discontinuation of the study. To prevent this, you will be asked to rinse once per day with an anti-fungal medication, nystatin suspension. However, should oral yeast infection occur, you will be given a full course of medication that works in yeast infections. This will not prevent you from continuing in the study.

Less Likely

- Adrenal suppression: Problems associated with the adrenal gland are very rare (<1%) with topically applied steroids. Cases of adrenal suppression from topically-applied steroid creams have been reported in young children and adults. In some cases, the cream was applied too frequently, and the thinner skin of children was felt to enhance systemic absorption. In other reports, it was difficult to determine if there was true adrenal suppression. In this study adrenal function will be assessed at the beginning and the end of the study. Given the relatively short duration of this study, we do not expect side effects.
- Viral Reactivation: Local immunosuppression in the mouth from topical corticosteroid use may allow certain viruses present in your body, including herpes simplex virus, to reactivate in the mouth or elsewhere in your body. Symptoms of oral viral reactivation include oral ulcers and oral pain, similar to symptoms of oral cGVHD. You will be monitored for viral activity during the study. If reactivation is detected, you will be treated systemically with anti-viral medication.

Rare but Serious

- allergic reaction
- thinning of the lining of the mouth
- dilation of the small blood vessels in the mouth (spider veins).
- Very rare side effects possible with an individual with extensive internal absorption include acne-like skin rash, cataracts, bruising, water retention, heartburn or stomach upset, swelling of the parotid (large salivary glands) stomach ulcer, glaucoma, increased

body hair, high blood pressure, decreased blood potassium, hypopigmentation or other changes in skin pigmentation, and unusual loss of hair. These are side effects usually seen with systemic steroids, and are not expected with the topical steroid treatment used in this study.

Unknown side effects: You might also develop a side effect that hasn't yet been reported. Please tell us about any changes in your health that develop during and after your participation in this study. Treatment will be interrupted, delayed, or stopped if you develop any serious side effect. All complications from this treatment will receive full and prompt medical attention from NIH Clinical Center staff. You will be told of any newly reported risks that may affect your decision to continue in the study.

Because evaluation the safety of the oral rinse is one of the endpoints of this study you will be asked to evaluate your symptoms and any side-effects at follow-up visits. You will be asked to keep a medication diary to record when you take the study medication and any additional medications or side effects you experience while on this study. The study nurse or investigator will meet with you every month to review your progress and the medication diary.

Related to Oral Biopsy:

Oral biopsy is a minor surgical procedure that is performed under local anesthesia.

Likely

- Expect a minor degree of soreness. This generally goes away in a couple of days.

Rare but Serious

- Bruising and infection at the biopsy site. These are generally rare (<5%).

Related to blood testing: Collection of blood will be done primarily in association with post-transplant sampling.

Likely

- Some discomfort: You will feel a little needle pinch at the site the needle is inserted.
- Pain and bruising in the area where the blood was drawn.
- Lightheadedness, or on a rare occasion fainting

Related to Saliva collection: There is no associated risk or discomfort.

Related to ACTH Stimulation Test: Side effects of a single ACTH injection are rare, but may include changes in heart rate, increased blood pressure, dizziness, and pain at the injection site.

Risks regarding pregnant or nursing women: It is not known whether clobetasol can harm pregnant women or nursing babies. Pregnant women or women who are breast-feeding may not take part in this study. Women who are participating in this study must be using effective

methods of birth control during their enrollment in this study. Effective methods include abstinence, surgical sterilization, barrier methods (such as diaphragm, condom, cervical cap, and sponge), birth control pills, and Depo-Provera.

Potential Benefits of Participation

The aim of this study is to see if this experimental clobetasol mouth rinse will be beneficial in treatment of oral GVHD. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include healing of oral ulcers or lessening of your symptoms, such as pain, that are caused by the oral GVHD. There may be indirect benefits associated with thorough oral examinations performed in the study. Because there is not much information about clobetasol's effect in this form on oral cGVHD we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have chronic GVHD.

Alternative Approaches or Treatments

We do not know whether the treatment used in the study will have any effect (good or bad) on your disease. If your disease worsens after two weeks of treatment with clobetasol you will be taken off study and offered alternative treatment.

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options:

- Getting treatment or care for your oral cGVHD without being in a study. Alternative treatment for oral GVHD includes other topical or systemic steroids and systemic immunosuppressive drugs.
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain and other problems caused by oral cGVHD. It does not treat oral cGVHD directly.

Please talk to your doctor about these and other options.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if we determine that your oral condition worsened at the 2 week of receiving clobetasol rinse
- if a change in systemic immunosuppression is necessary to control GVHD outside the mouth in the first 2 weeks of the study
- if you have side effects from the treatment that your doctor thinks are too severe

- if study if you are unable to follow the study procedures and evaluations.
- if new information shows that another treatment would be better for you
- if the study doctor decides to end the study

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Spectrum Chemicals or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Optional Blood Tests

We would like measure the rate at which the study drug reaches the bloodstream after one two-minute rinse in a subset of patients. This would involve a single appointment at which you would rinse with the study drug for 2 minutes, and then a small blood sample would be taken at 0 minutes, 15-45 minutes, and 90-120 minutes after rinsing. This would be done at the same visit as one of your scheduled study visits. We do not expect that much of the study drug will reach the bloodstream, however it will provide valuable information to know how quickly this occurs. This information will help us screen patients in this study for side effects, and will improve the design of future treatments.

You will be given the chance to decide if you want to participate at the time of the procedure. No matter what you decide to do, it will not affect your care or study participation.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.
We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Steven Pavletic, M.D., Building 10, Room 3-3330 Telephone: 240-760-6174. You may also call the Clinical Center Patient Representative at (301) 496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM AUGUST 22, 2016 THROUGH AUGUST 21, 2017.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____